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PANCREATITIS*

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PROGRESS in the diagnosis and treatment of pancreatitis has not been as satisfactory as that in many other common conditions. The inaccessible location of the pancreas has made both physical and radiologic examination unsatisfactory unless a large cyst or tumor mass is present. The retroperitoneal position of the pancreas, like that of the kidney, is responsible for the often bizarre and variable signs and symptoms. It is now recognized that repeated acute attacks of pancreatitis in the same patient are common and may have been misinterpreted or overlooked until calcific deposits are demonstrated in the region of the pancreas during x-ray investigation of undiagnosed abdominal pain. The treatment of acute interstitial pancreatitis has been fairly well standardized. However, there is little agreement concerning the successful management of chronic recurrent or calcific types of this disease and the mortality remains relatively high. Both acute and chronic forms of pancreatitis are more common than observers formerly believed. The frequency of diagnosis appears to be related directly to the degree of suspicion regarding this disorder in the differential diagnosis of abdominal pain and its confirmation by early blood amylase determinations.[1,2]

ACUTE PANCREATITIS

Diagnosis

The clinical picture of acute pancreatitis is quite variable and often confusing, and the diagnosis cannot be established without laboratory confirmation. Pain, however, is a constant complaint. Clinical and experimental studies of this symptom have proved of considerable interest.[3] Direct stimulation of the pancreas by means of very fine electrodes inserted into the head, body and tail was performed during the postoperative period in a series of patients subjected to elective biliary-tract surgery. It was found that pain resulting from stimulation of the head of the pancreas was distributed over the right epigastrium, that from stimulation of the body to the midepigastric region and that from stimulation of the tail to the lower epigastrium on the left and at times even into the left lower quadrant. Simultaneous stimulation of all three areas produced bandlike pain across the epigastrium, with radiation to the back. It should be remembered, therefore, that segmental involvement and reference of pain from the head, body and tail of the pancreas may produce symptoms mimicking many other lesions within the peritoneal cavity. It is probable that the patient complains of the so-called typical bandlike pain extending across the upper abdomen only when the entire organ is diffusely inflamed.

Although the symptomatology often suggests the diagnosis the single most useful diagnostic procedure is the blood amylase test.[4] Only by its routine emergency use in patients with abdominal pain does the physician appreciate the frequency of pancreatitis. The frequency of diagnosis of pancreatitis, therefore, parallels that with which the physician considers it and obtains a blood amylase determination, which seems to be as valuable as a white-cell count in patients with upper abdominal pain. Since early operation for acute pancreatitis contributes nothing and may add to the morbidity and mortality of the disease, correct diagnosis is imperative.[5-7]

Unfortunately, blood amylase levels usually remain elevated for only two or three days and are frequently not diagnostic by the third day.[8] However, amylase values of peritoneal fluid remain elevated two to four days longer.[9] Patients seen three or four days after the onset of abdominal pain with normal or equivocal blood amylase values often present difficult diagnostic problems. In these cases a small amount of peritoneal fluid may be aspirated from the peritoneal cavity through a 20-gauge needle inserted through the midline of the abdomen just

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below the umbilicus. The amylase value of this peritoneal fluid is frequently so high that even small amounts of fluid can be diluted sufficiently for amylase determination. A value of 300 Somogyi units or more confirms the diagnosis. No complications have occurred as a result of this procedure, which is considered a useful diagnostic test in baffling problems of acute abdominal pain. If a sufficient amount of fluid is aspirated testing for the presence of bile and total hydrochloric acid may further distinguish pancreatitis from perforated ulcer.

Blood amylase should also be measured in patients with gall-bladder attacks, injuries to the upper abdomen and bizarre abdominal pain associated with distention, as well as abdominal complications after surgery on the upper abdomen.[10] These determinations will show pancreatitis to be common and will convince the physician of the value of utilizing this test more frequently, day or night, than has commonly been the practice in the past.

There are often significant roentgenologic findings in pancreatitis, and their recognition is of definite diagnostic aid. Three things should be carefully sought in the interpretation of plain films of the abdomen. These are paralytic ileus, gallstones and areas of calcification in the region of the pancreas. There is often a single, gas-filled sentinel loop of small intestine in the midportion of the abdomen[11] or a segmental type of ileus with several areas of gas-filled intestine. Plain films of the abdomen should be carefully reviewed for gallstones, which are occasionally seen; biliary-tract disease is present in over 50 per cent of patients with pancreatitis. If calcification is visualized in the pancreas the diagnosis of chronic, calcareous pancreatitis with an acute exacerbation is strongly suggested. After an acute attack has subsided additional information may be obtained by barium meal. The duodenal "C" loop is often widened, the greater curvature of the stomach may be elevated and flattened, and there is often anterior displacement of the stomach. The extensive inflammatory process in the lesser sac at times results in a shaggy, edematous appearance in the mucosa of the stomach and duodenum. Owing to lymphatic interchange it is not unusual to find a pleural effusion in the left lower portion of the chest on x-ray examination.[12]

Therapy

There is general agreement that the initial treatment of acute pancreatitis should be conservative and that surgery in this stage of the disease results in an increase in morbidity and mortality. The basic aim of therapy is to put the pancreas at physiologic rest by reducing the external pancreatic secretion to a minimum. This objective is attained by controlling both the hormonal, or secretin, mechanism and the cephalic secretory phase. However, the first obligation of the physician is to relieve pain. Demerol rather than morphine has been recommended on the assumption that it produces less spasm of the sphincter of Oddi, thereby allowing better drainage of pancreatic secretions.[13] If the pain is difficult to control splanchnic blocks may be utilized, and some have recommended leaving a small ureteral catheter in the epidural space, permitting continuous anesthesia.[14] Actually, we have seldom found it necessary to use splanchnic blocks in recent years, since more attention has been given to putting the pancreas at rest. There is ample experimental evidence to support the clinical practice of attempting to neutralize gastric acidity since contact of gastric juice with the duodenal mucosa releases secretin, which stimulates the pancreas, producing an increase of secretion rich in enzymes. Not only should food be withheld from these patients with pancreatitis but also gastric suction should be instituted immediately, to control the tendency to abdominal distention and to remove as much of the gastric juice as possible. Both gastric and pancreatic secretions may be further depressed by the use of atropine, Banthine and Probanthine.

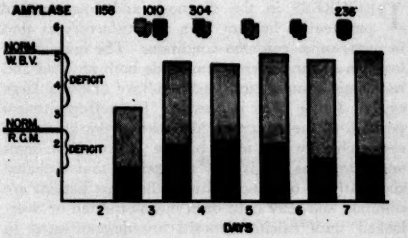

FIGURE 1. *Correction of the Marked Blood-Volume Deficits Found in a Case of Severe Acute Pancreatitis. Replenishment would be more ideal with more whole blood and less albumin. Each small flask represents 100 cc. of serum albumin. Each large black flask represents 500 cc. of whole blood. (W.B.V.—whole-blood volume; R.C.M.—red-cell mass.)*

An important but commonly neglected aspect of treatment is the restoration of blood volume. Blood-volume studies have shown that there is an extensive loss of plasma and red cells from the circulation in patients with pancreatitis (Fig. 1). Twelve patients with acute and 16 with chronic pancreatitis recently studied have shown an average whole-blood-volume deficit of 30 per cent, which is equivalent to about 1500 cc.[15]

Such deficits have been found with regularity during acute attacks, despite a normal or elevated hematocrit, hemoglobin and red-cell count. Fluids and electrolytes are necessary to correct the concomitant dehydration, but the continuing and often unrecognized deficits in blood volume and total circulating plasma proteins are not altered. Clinical

findings of persistent abdominal distention, pain and an elevated pulse rate suggest such a deficit.

Human serum albumin is now readily available from the American Red Cross. It is an effective agent for augmenting plasma proteins and circulating plasma volume and is free from the danger of hepatitis inherent in the use of plasma and whole blood. Kenwell and Wels[16] have recommended that these patients receive albumin daily in amounts of 300 to 500 cc. for at least three to five days. They postulate that the beneficial effect of the albumin is related to its capacity to inhibit trypsin. Our practice is to give 200 cc. of albumin to these patients as soon as the diagnosis of pancreatitis has been made. This amount is repeated each day until the plasma volume has returned to normal (Fig. 1). As much as 12 units or 1200 cc. of albumin has been given to patients with acute pancreatitis over a five-day period. Recent experimental work in our laboratories, however, tends to show that the value of serum albumin is more closely related to restoration of depleted plasma volume than to its antitryptic effects, as measured by antifibrinolysin titers.[17] Similar deficits are found in the red-cell mass, which should be corrected with whole blood despite normal or only slightly lowered peripheral blood counts.

Antibiotics are valuable adjuncts in cases of pancreatitis with biliary-tract complications but are even more effective in prophylaxis against secondary infection. Chlortetracycline and oxytetracycline are probably the antibiotics of choice since they are concentrated in bile.[14]

In approximately 40 per cent of patients with pancreatitis there is evidence of glycosuria or hyperglycemia. In acute pancreatitis this may be transitory, whereas in the chronic type sufficient destruction of pancreatic tissue may result in a true diabetes mellitus. For this reason, insulin may be required. However, excessive amounts of insulin may produce hypoglycemia, resulting in increased secretion of free hydrochloric acid, which in turn stimulates the pancreas. Therefore, overdosage of insulin should be rigidly avoided in patients with pancreatitis.

It has been recognized that hypocalcemia may occur, particularly in severe acute pancreatitis. A serum calcium level below 7.5 mg. per 100 cc. may denote a poor prognosis.[18] It seems logical to give 1 gm. of calcium gluconate intravenously a day to patients with lowered calcium levels.

In summary, treatment of the usual case of acute pancreatitis consists of relief of pain with Demerol or splanchnic blocks; prolonged gastric suction; large doses of vagal-blocking drugs; restoration of blood volume; and correction of any other metabolic alterations. The mistakes most frequently made in the management of the acute attack are premature abandonment of gastric suction and failure to re-establish normal blood volumes. Oral feeding should be withheld for at least forty-eight hours after the subsidence of symptoms lest a recurrent attack is precipitated. After recovery from the acute episode the patient should be discharged, with instructions to continue antacids and to abstain from overeating. Coffee, alcohol and other agents known to stimulate gastric acid secretion are to be avoided. After following this regimen for about six weeks the patient should return for a cholecystogram[19] and barium study of the upper gastrointestinal tract. In the event that gall-bladder disease is found, it should be corrected. If gall-bladder disease is demonstrated by the presence of radiopaque calculi during the acute attack, there seems to be no contraindication to biliary surgery shortly after symptoms have subsided and the patient has recovered. During surgery for concomitant biliary disease careful exploration of the common duct is essential and is rewarded by the finding of stones in a significant number of cases.

Chronic Pancreatitis

Most patients surviving acute pancreatitis will not have succeeding attacks, particularly if existent biliary-tract disease is removed.[20] However, recurrent or chronic pancreatitis will develop in an appreciable number, the criteria, in this clinic, being three attacks, calcification on roentgenographic examination or confirmation by biopsy. Medical management of these patients is usually futile, and surgical intervention must be considered.

Any surgical procedure designed for diagnosis or treatment of chronic pancreatitis should invariably include a careful inspection of all parts of the pancreas under direct vision. When a pseudocyst is found it may be drained or resected. Cholelithiasis, if still present, is treated by cholecystectomy, after which the cystic-duct stump is utilized for operative cholangiography. This is of considerable value in demonstrating common-duct stones, obstruction due to encroachment by fibrosis or induration of the head of the pancreas and biliary reflux via a "common channel." If the last is demonstrated on the cholangiogram, a transduodenal sphincterotomy should be done. In the absence of a demonstrable common channel or extensive calcification, and particularly when no biliary-tract disease has been found, an indirect approach such as vagotomy combined with partial gastric resection, including at least the entire antrum, may be worth while. The presence or history of recent jaundice or demonstration of intrapancreatic common-duct obstruction indicates the addition of a biliary shunt to the procedure if no common-duct stones are found. These principles are illustrated by the cases presented below.

Case Reports

J.F. (517493A), a 39-year-old man, had complained of incapacitating epigastric pain for 9 years. He had been treated for suspected duodenal ulcer for several years without response and had become an alcoholic. During the year before admission severe pain had followed almost every

meal, and as a result he had lost 45 pounds in weight. In addition gradually progressive jaundice and diabetes mellitus had developed.

Diffuse calcification in the area of the pancreas on x-ray examination confirmed the suspected diagnosis of chronic pancreatitis. This calcification and a distended gall bladder were demonstrated at operation. A vagotomy, 50 per cent gastric resection with Hofmeister anastomosis and a cholecystoduodenostomy were performed. In the interim of 2½ years since the operation he has had no further attacks of pain, has returned to work and has gained a limited amount of weight.

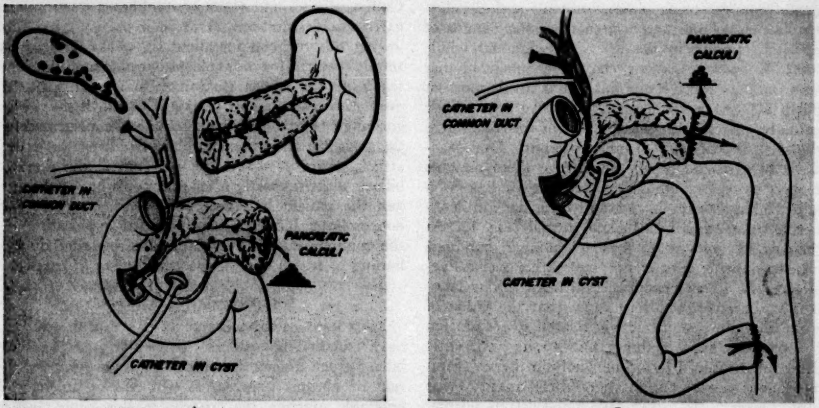

FIGURE 2. *Diagrams Representing the First* (A) *and Second* (B) *Surgical Procedures on C. H. Note sphincterotomy, catheter in pseudocyst, resection of the tail of the pancreas, removal of calculi from the dilated pancreatic duct and closure of the duct* (A); *the previously ligated duct is reopened and anastomosed to a Roux-Y loop of jejunum* (B) *after remaining calculi had been removed.*

A more formidable surgical challenge was presented by the following case:

C.H. (534316X), a 38-year-old Negro, complained of recurrent acute attacks of severe epigastric pain that radiated to the back and were usually precipitated by eating. These attacks had occurred intermittently over the past 5 years, usually required repeated doses of narcotics, no longer responded to any treatment and had resulted in alcoholism and total incapacitation. He had lost 20 pounds in weight during the 3 months before admission.

On admission he had an elevated blood amylase, diffuse calcification in the area of the pancreas and multiple calculi on a cholecystogram. At operation, after the acute attack had subsided, these findings were confirmed. The gall bladder was removed, the common duct explored, and an operative cholangiogram was obtained. The common duct was found to be considerably narrowed as it passed through the enlarged, indurated head of the pancreas, which contained a pseudocyst 5 cm. in diameter. A transduodenal sphincterotomy was performed; several calculi were removed from the pancreatic duct, and a polyethylene tube was successfully passed through this duct into the communicating pseudocyst. The pancreatic duct was greatly dilated and contained many additional stones throughout its entire length. Consequently, the tail of the pancreas was resected to allow retrograde irrigation of the pancreatic duct and removal of these calculi. Numerous stones were recovered, and the severed distal end of the duct was closed (Fig. 2*A*). Subsequent injection of Diodrast through both the polyethylene tube and the catheter demonstrated continued dilatation of the pancreatic duct, which still contained several calculi.

After a relatively uneventful convalescence the patient improved but continued to have milder attacks. Since there are experimental and clinical indications that retrograde pancreatic drainage is feasible[31-33] it was decided to attempt an anastomosis of the previously ligated distal pancreatic duct to the jejunum (Fig. 2*B*). This was successfully accomplished by reopening of the duct and anastomosis of the transected end of the body of the pancreas to the open end of a Roux-Y loop of proximal jejunum. During this procedure, which was performed 3 months after the previous operation, several additional stones were removed from the further enlarged pancreatic duct. Since the 2d operation the patient has been relatively free of pain, has gained weight and has returned to work.

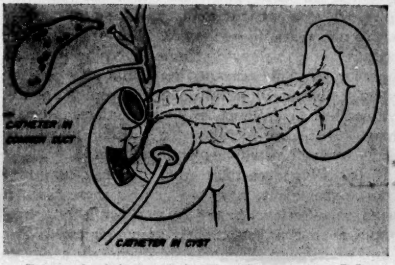

FIGURE 3. *Scheme of the First Operation on R.P. Note sphincterotomy and catheter in the pseudocyst communicating with the pancreatic duct, which was considerably dilated distal to this point.*

Virtually the same problem was presented by the following case:

R.P. (539626A), a 26-year-old man, had similar symptoms of 2 years' duration. At his 1st operation cholecystectomy and common-duct exploration, with operative cholangiogram and sphincterotomy, were performed. In addition

a large cyst found in the head of the pancreas was drained externally by introduction of a mushroom catheter (Fig. 3). The cholangiogram showed slight reflux into the pancreatic duct, but subsequent injection into the cyst through the catheter disclosed considerable dilatation of the pancreatic duct, with very little drainage through the previously sectioned sphincter (Fig. 4). Because of this finding, together with incomplete relief of symptoms, a 2d operation, consisting of resection of the tail of the pancreas and end-to-side anastomosis of the dilated duct to the jejunum, was performed (Fig. 5). Subsequent injection of Diodrast through the catheter into the cyst not only showed the anastomosis to be patent but also emptied more contrast medium than the pancreatic duct through the sectioned sphincter (Fig. 6). Although the 2d operation was recently performed the patient has remained symptom free and has returned to work.

FIGURE 4. *Subsequent Injection of Contrast Medium into the Cyst in R.P., Showing Communication with and Filling of the Dilated Pancreatic Duct but Little Drainage through the Sectioned Sphincter.*

A current project in the surgical laboratory is concerned with investigating the feasibility of retrograde anastomosis of obstructed pancreatic ducts to the jejunum by both end-to-side and Roux-Y technics.[24]

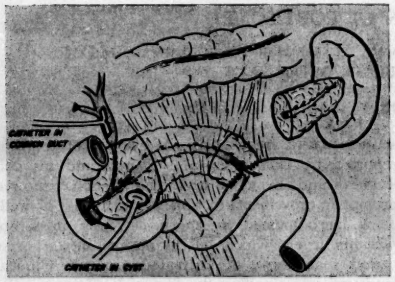

FIGURE 5. *Second Operation on R.P. Note excision of the tail of the pancreas and retrograde end-to-side pancreaticojejunostomy, utilizing the dilated pancreatic duct.*

DISCUSSION

Pancreatitis is now considered a frequent cause of both acute and chronic abdominal pain. Many other common abdominal lesions may be simulated by the variable and sometimes bizarre manifestations of the disease, which requires alertness on the part of the examiner and laboratory confirmation for accurate diagnosis. The single most important diagnostic aid is a blood amylase determination obtained within the first forty-eight hours. Routine use of this test on an emergency basis in all patients with acute abdominal pain will afford a diagnosis with remarkable frequency. In suspected cases of longer duration, with equivocal or normal blood amylase values, analysis of peritoneal fluid obtained by a simple peritoneal tap often establishes the diagnosis. The finding of a "sentinel loop" or segmental ileus, displacement of surrounding viscera, gallstones or calcification in the pancreas on roentgenologic examination furnishes further valuable diagnostic information.

FIGURE 6. *Injection of Diodrast through the Catheter in R.P.*

The optimum management of the acute phase is conservative, and its purpose is to place the pancreas at physiologic rest and simultaneously to correct the usual blood-volume deficits and metabolic alterations. If biliary-tract disease is known to exist or is demonstrated at this time, it should be corrected after the acute episode has subsided. Continued management is directed toward a sustained effort both to inhibit mechanisms of pancreatic secretion by diet and vagal-blocking drugs and to detect the patients with concomitant biliary-tract disease.

Blood-volume studies on patients with all types of pancreatitis have shown impressive and frequent deficits. The importance of replenishing these deficits with equivalent volumes of serum albumin and whole blood cannot be overemphasized.

Success in the definitive surgical treatment of chronic pancreatitis depends on careful selection of one or more procedures based on the problems presented by the individual patient rather than adoption of a "standard operation." This selection requires extensive and careful study of the existent pathology and the most likely mechanisms of its pathogenesis.

Sphincterotomy, vagotomy, partial gastrectomy and biliary shunts all have a sound physiologic basis and a definite place in the management of chronic pancreatitis so long as they are appropriately utilized for specific indications. Both clinical and experimental results obtained by direct retrograde anastomosis of the pancreatic duct to the jejunum have been encouraging and merit further investigation. Clinical results with utilization of these principles in the management of all types of pancreatitis are summarized in Table 1, which demonstrates the high

TABLE 1. *Results in the Management of All Types of Pancreatitis, January, 1947, to January, 1954.*

TYPE OF PANCREATITIS	NO. OF CASES	NO. OF DEATHS	MORTALITY
			%
Acute (primary)	74	3	4.0
Postoperative	21	10	47.6
Traumatic	5	1	20.0
Chronic*	34	3	8.5
Totals	134	17	
Average			12.6

*3 previous attacks, calcification or biopsy.

mortality in postoperative as compared with primary pancreatitis.

CONCLUSIONS

Emergency blood amylase levels should be obtained in all patients with pain in the upper abdomen, "gall-bladder attacks," injuries to the upper abdomen and complications after operations on the upper abdomen.

Blood-volume deficits should be replenished with serum albumin and whole blood.

An individualized surgical approach is indicated in chronic pancreatitis.

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CHOLERETIC ACTION OF CORTISONE*

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BOSTON

ACTH and cortisone have had extensive therapeutic trials in the management of acute and chronic diseases of the liver. Most patients with acute hepatitis treated with ACTH or cortisone, as reported by Colbert et al.,[1] Sborov and his colleagues[2] and Evans, Sprinz and Nelson,[3] showed prompt improvements in appetite and sense of well-being, accompanied by sharp decreases in serum bilirubin levels, which fell to normal in a shorter period than those of untreated groups.[2] Clinical remission was significantly hastened. However, the frequency and severity of complications that occurred during administration and the relapses after withdrawal limit the usefulness of these agents in the management of acute hepatitis.

The majority of patients with chronic liver disease treated with ACTH and cortisone, according to Havens, Myerson and Carroll,[4] Gyorgy and Bluemle[5]

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and Bongiovanni and Eisenmenger,[6] had partial, temporary improvement in symptoms and in liver-function tests. All the foregoing groups noted some decreases in serum bilirubin levels, a reduction in bromsulfalein retention and an increase in urinary urobilinogen excretion during hormone therapy. These changes were interpreted as indicating improvement in the metabolism of bile pigments. Williams and Flink[7] have shown, in a group of patients with cirrhosis and pruritus, that ACTH therapy produced a fall in elevated bile acid levels in the blood that paralleled the relief of pruritus. The effect on the level of serum bilirubin was variable, and there was no consistent change in fecal and urinary urobilinogen excretion. These authors suggest that the lowering of the level of bile acids during ACTH administration may reflect the diversion of these substances into the synthesis of adrenocortical hormones.

The reduction in elevated serum bilirubin levels frequently noted in patients with liver disease treated with either ACTH or cortisone is illustrated by a patient with cholangiolitic cirrhosis who was given both ACTH intramuscularly and cortisone intravenously by continuous infusion (Fig. 1). With either hormone there was a prompt fall in the serum bilirubin, followed by a rise to previous levels when hormone therapy was discontinued. The decline in serum alkaline phosphatase that occurred with hormone therapy suggested an increase in biliary flow.

The mechanism of the lessening of icterus in patients receiving hormone therapy has been ascribed to an "anti-inflammatory" action of adrenal steroids on the diseased liver. Since the adrenal steroids and cholic acids have similar chemical configurations (cortisone is commercially synthesized from desoxycholic acid) an additional explanation may be that the action is one of simple choleresis similar to that of bile salts on hepatic biliary flow.

The purpose of the present study was, therefore, to demonstrate whether or not cortisone had a significant choleretic effect on the liver. This was determined by measurement of the influence of intravenously and duodenally instilled cortisone on the volume and bilirubin content of duodenal fluid.

Methods

Duodenal aspiration was performed on 9 adults and 6 children. Six were normal adults; the remainder of the subjects were patients on the wards of the Children's Medical Center and the Peter Bent Brigham Hospital.

Duodenal intubations were performed under fluoroscopic visualization. After the gastric contents had been aspirated, the tip of a Levin tube was placed at the lower end of the second portion of the duodenum. Duodenal fluid was then collected at fifteen-minute intervals by gravity flow for periods of five to seven hours. The samples were measured, and the color, pH, viscosity, chloride and pancreatic enzyme activity were subsequently determined. The bilirubin concentration was estimated by the method of Malloy and Evelyn.[8] The icteric index was measured colorimetrically by use of the duodenal fluid diluted 1:100 with distilled water with filter of 420 microns in the Klett-Summerson colorimeter. The scale readings were recorded as a measure of bile concentration. The pH was estimated with pHydron papers* (error ±0.2). The viscosity was calculated in an Ostwald viscosimeter of 3-cc. capacity with a

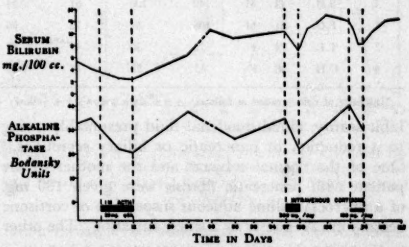

Figure 1. *Effect of ACTH by Intramuscular Injection and Cortisone by Intravenous Infusion on the Serum Bilirubin and Alkaline Phosphatase Levels in Biliary Cirrhosis.*

flow time of thirty-three seconds with distilled water at 20°C.[9,10] Chlorides were determined by the Van Slyke method, as modified by Wilson and Ball.[11] Trypsin was measured by three technics: the Andersen and Early[12] modification of the Fermi procedure, with gelatin as a substrate, and the turbidimetric and formal titration methods modified by Leubner,[13] with casein as a substrate. Amylase was calculated by a starch turbidity method[14] and by the technic of Free and Myers,[15] in which the sugar liberated from starch digestion is measured. Lipase was determined in two ways — by the use of olive oil[16] and tributyrin[18] as substrates. The carboxypeptidase procedure was that of Ravin and Seligman.[17]

Observations

Normal Subjects

Continuous duodenal drainage in 4 normal adults who served as controls revealed a progressive decline in the volume of the duodenal fluid over a period of collection of four or five hours, the value being greatest during the first hour (Table 1). Characteristically, the color of the fluid changed from that of a dark yellow or amber, initially, to pale yellow or colorless after prolonged drainage, indicating not only a decrease in volume but also a decline in the total bile-pigment content of the fluid with time.

After a control collection of duodenal fluid for

*Obtainable from Micro Essential Laboratory, Brooklyn 10, New York.

one or two hours cortisone was given intravenously to 2 other normal subjects, and to the mother of a child with pancreatic fibrosis (Table 2, Cases 5-7). Although the mother had no symptoms or signs of illness preliminary observations indicate that parents of children with pancreatic fibrosis occasionally exhibit scanty, viscid duodenal fluid presumably owing to a reduction in pancreatic or biliary secretions.[18] One of the normal subjects and the mother of the patient with pancreatic fibrosis were given 100 mg. of a microcrystalline aqueous suspension of cortisone acetate intravenously as a single injection. The other normal subject received a two-hour intravenous infusion of 100 mg. of cortisone (free alcohol) dissolved in 5 per cent dextrose and water with 1 per cent ethyl alcohol.[19]

Table 1. *Effect of Continuous Duodenal Drainage on the Volume and Appearance of Duodenal Fluid in Normal Subjects.*

Case No.	Initial	Age	Sex	Volume of Duodenal Fluid					Color of Duodenal Fluid*				
				1st hr. of drainage	2d hr. of drainage	3d hr. of drainage	4th hr. of drainage	5th hr. of drainage	1st hr. of drainage	2d hr. of drainage	3d hr. of drainage	4th hr. of drainage	5th hr. of drainage
		yr.		cc./hr.	cc./hr.	cc./hr.	cc./hr.	cc./hr.					
1	S.H.	42	M	140	100	61	54	51	+++	+++	+	+	+
2	F.G.	31	M	106	84	72	66	61	+++	++	++	+	+
3	T.L.	24	F	72	50	42	27	20	++	++	+	+	0
4	C.H.	28	F	45	32	28	25	—	++	+	0	0	–

*Intensity of color graded as follows: +++ dark yellow; ++ yellow; + light yellow; 0 colorless.

A moderate secondary rise four and five hours later. The third subject had scanty viscid fluid, with a low icteric index in the fasting state. A moderate increase in volume and bile content followed psychic stimulation from observation and smelling of food, but a striking rise in icteric index occurred in the second hour after cortisone was given. There was a further increase in pigment content as well as a large increase in hourly volume in the fourth and fifth hours. The abnormally high viscosity of the fluid (eight minutes) fell to normal levels (one minute and thirty seconds) after the initiation of choleresis.

Table 2. *Effect of Intravenous Administration of Cortisone on the Volume and Bile Concentration of Duodenal Fluid in Normal and Diseased Subjects.*

Case No.	Initial	Age	Sex	Diagnosis	Dosage of Cortisone*	Volume of Duodenal Fluid†						
						2 hr. before cortisone	1 hr. before cortisone	1 hr. after cortisone	2 hr. after cortisone	3 hr. after cortisone	4 hr. after cortisone	5 hr. after cortisone
		yr.			mg.	cc./hr.	cc./hr.	cc./hr.	cc./hr.	cc./hr.	cc./hr.	cc./hr.
5	M.M.	22	M	Normal subject	100	164	228	143	102	109	113	93
6	B.W.	25	F	Normal subject	100		21	101	43	29	55	55
7	M.B.	27	F	Normal subject§	100	12	40¶	28	13	12	76	85
8	M.W.	33	F	Chronic pancreatitis; nonfunctioning gall bladder.	100	14	17	55	24	53		
9	R.F.	45	F	Postcholecystectomy syndrome	100	39	48	64	54	58	57	33
10	D.D.	6	F	Rheumatic fever	50	13	33¶	14	31	13		
11	A.F.	15	F	Infectious hepatitis	100	50	22	82	37	34	94	

*Cortisone acetate microcrystalline suspension, given intravenously in 5-min. period except in Case 5, in which 2-hr. intravenous infusion of 100 mg. of cortisone (free alcohol) dissolved in 500 cc. of 5 per cent dextrose & water, with 1 per cent ethyl alcohol.
†15-min. collection periods.
‡Highest value observed in any 15-min. period during each hr. recorded as representative of bile concentration present for that period.
§Mother of infant with pancreatic fibrosis; duodenal fluid viscid, scanty & light colored before cortisone administration.
¶Stimulation of flow due to observation & smelling of food.

Both normal subjects evidenced a substantial and prolonged increase in bilirubin concentration of the duodenal fluid after intravenous administration of cortisone, suggesting a choleretic effect of this steroid. The hourly volume fell off gradually from an initial high value in the first subject, increasing sharply in the first hour after administration in the second subject, with a moderate secondary rise four and five hours later. The third subject had scanty viscid fluid, with a low icteric index in the fasting state. A moderate increase in volume and bile content followed psychic stimulation from observation and smelling of food, but a striking rise in icteric index occurred in the second hour after cortisone was given. There was a further increase in pigment content as well as a large increase in hourly volume in the fourth and fifth hours. The abnormally high viscosity of the fluid (eight minutes) fell to normal levels (one minute and thirty seconds) after the initiation of choleresis.

Patients

The response to cortisone was studied in 8 patients. Three adults and 1 child received 50 to 100

mg. of the acetate microcrystalline suspension intravenously after a control duodenal drainage of one or two hours (Table 2, Cases 8-11). Four children received the cortisone suspension intraduodenally through the Levin tube (Table 3).

A patient with chronic pancreatitis and a nonfunctioning gall bladder documented by repeated cholecystograms evidenced an increase of both bilirubin concentration and volume of flow after cortisone administration (Table 2 and Fig. 2). Likewise, a patient with a postcholecystectomy syndrome, in whom gall-bladder function could not contribute to the output of bile, manifested an increase in hourly volume and bilirubin concentration after hormone injection. This suggests that the action of cortisone is not due solely to a stimulating effect in emptying the gall bladder. A child with quiescent rheumatic fever given cortisone intravenously did not show an increase in volume equal to that observed with food stimulation, but did have a substantial increase in the concentration of bilirubin in the duodenal fluid. In a patient with acute infectious hepatitis injection of the hormone was accompanied by a prompt rise in both the volume and the bilirubin concentration of the duodenal fluid; a second-

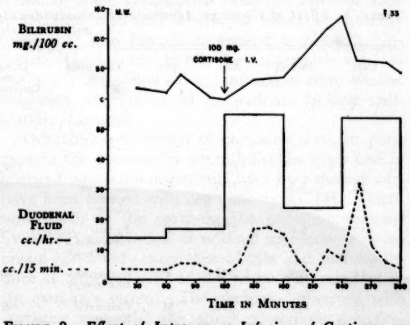

FIGURE 2. *Effect of Intravenous Infusion of Cortisone on the Volume and Bilirubin Concentration of Duodenal Fluid in a Patient with Chronic Pancreatitis and a Nonfunctioning Gall Bladder.*

observed at the end of the second hour after cortisone administration were not sustained. In 1 the increase did not equal that seen with psychic stimulation initiated by observation of food but was much higher than the resting control level. Although a

TABLE 2 *(Concluded).*

CASE No.	BILIRUBIN‡							ICTERIC INDEX				
	2 HR. BEFORE CORTISONE	1 HR. BEFORE CORTISONE	1 HR. AFTER CORTISONE	2 HR. AFTER CORTISONE	3 HR. AFTER CORTISONE	4 HR. AFTER CORTISONE	5 HR. AFTER CORTISONE	2 HR. BEFORE CORTISONE	1 HR. BEFORE CORTISONE	1 HR. AFTER CORTISONE	2 HR. AFTER CORTISONE	4 HR. AFTER CORTISONE
	mg./100 cc.	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*					
5	2.8	2.0	0.1	31.4	24.1	7.1	16.0					
6		41.6		8.1	5.6	10.6	12.6					
7								26	93	28	199	296
8	1.7	4.0	3.8	13.7	6.3							
9	7.3	9.4	10.1	13.5	9.5	13.4	10.7					
10	0.2	8.1	0.9	17.3	42.1							
11	25.5	42.9	49.7	71.7	22.0	35.1						

ary rise in volume in the fourth hour was accompanied by a decline in the pigment concentration.

Since the bilirubin concentration of the duodenal fluid obtained during these studies was measured on selected fifteen-minute specimens only it is not possible to calculate the total bilirubin output in milligrams per hour before and after cortisone. However, calculation of total bilirubin elaborated during these fifteen-minute periods reveals that, in 5 of the 7 patients, a definite sustained increase was observed after cortisone. In the remaining 2 patients increases striking rise in total bilirubin content was not observed after cortisone in these 2 patients, some choleretic effect probably occurred since the sharp decline in volume and pigment concentration seen after prolonged drainage in normal subjects not given cortisone was not observed (Table 1).

In 4 children the cortisone acetate suspension in doses ranging from 25 to 100 mg. was injected through the Levin tube into the duodenum after a one-hour control collection. The tube was then clamped, and two hours later another one-hour col-

lection was made. These children had various disorders of the digestive system characterized by large or frequent, foul stools; the fasting duodenal fluid was light colored, scanty and viscid. In all cases (Table 3) the high viscosity of the fluid fell to normal after cortisone administration. In 3 of the 4 children both the volume and the intensity of color of the aspirated fluid increased, indicating an increase in total bile flow.

Effect of Cortisone on Other Constituents of Duodenal Fluid

In addition to the increase in volume and in the concentration of bilirubin in the duodenal fluid that followed cortisone administration changes in pancreatic-enzyme activity were also noted (Table 4). Two normal adults (Cases 5 and 6) and 1 child with idiopathic celiac disease (Case 12) had normal duodenal enzyme activity, not influenced by cortisone.

Table 3. *Effect of Cortisone Administered Intraduodenally on Volume and Character of Duodenal Fluid in Children with Gastrointestinal Disease.*

Case No.	Initial	Age	Sex	Diagnosis	Dosage of Cortisone*	Volume of Duodenal Fluid		Appearance of Duodenal Fluid		Viscosity of Fluid†	
						Control hr.	3d hr.	Control hr.	3d hr.	Control hr.	3d hr.
		yr.			mg.	cc./hr.	cc./hr.			min.	min.
12	A.B.	3 4/12	F	Idiopathic celiac disease	25	14	46	Light yellow	Dark yellow	4	2
13	S.B.	3/12	F	Partial pancreatic insufficiency	50	3	7	Light yellow	Dark yellow	20	1
14	G.S.	1 2/12	F	Gastrointestinal allergy	50	8	16	Light yellow	Dark yellow	6	1
15	P.Y.	3/12	M	Pancreatic fibrosis	100	21	13	Yellow	Yellow	14	3

*Cortisone acetate microcrystalline suspension, administered through Levin tube after 1 hr. control collection; tube clamped & 1-hr. collection made 2 hr. later.
†Normal, less than 3 min.

Table 4. *Effect of Cortisone on Duodenal Enzyme Activity.*

Case No.	Dosage of Cortisone	Specimen No.	Interval after Cortisone Administration	Amylase*		Trypsin		Procarboxypeptidase	Carboxypeptidase	Lipase	
				Starch turbidity	Free-Myers method	Casein turbidity	Casein titration			Olive oil	Tributyrin
	mg.		min.								
5	100 (intravenously)	2	—	14	5.3	29	18	0.6	0.7	6.2	1.0
		9	—	22	3.3	31	23	0.3	0.3	3.5	1.4
		11	—	40	7.4	29	9	0.4	0.6	2.4	1.2
		15	60	22	3.1	24	3	0.0	0.2	3.6	0.6
6	100 (intravenously)	1	—	74	18	63	30	0.8	0.8	—	—
		6	15	34	8	52	16	0.5	0.6	—	—
		7	30	88	14	63	29	0.7	0.8	—	—
		18	195	94	14.5	66	38	1.5	1.5	—	—
7	100 (intravenously)	2	—	94	5	43	12	0	0.2	0.3	0.2
		20	180	101	6	34	14	0.7	1.1	0.1	0
		24	240	96	8	25	13	0.5	0.7	0.2	0
8	100 (intravenously)	1-6	—	0-0	0-0.4	0-2	0-7	0-0.1	0-0.2	0.6-1.6	0.1-0.2
		8-19	15-180†	0-4	0-1.2	0-8	0-7	0-0.02	0-0.1	0.5-2.2	0-0.1
10	50 (intravenously)	2	—	30	3	43	6	0.3	0.4	5.2	2.4
		4‡	—	46	4	26	8	0.9	0.9	6.4	2.5
		9	80	84	15	39	22	1.6	1.6	0.9	0.4
		11	120	98	16	63	35	1.6	—	0.6	0.4
12	25 (intraduodenally)	1	—	78	4.8	63	55	0.9	1.2	16	3
		4	180	—§	—§	—§					
13	50 (intraduodenally)	1	—	0	0.3	19	9	0	0	0.4	1.3
		2	120	3	0.1	60	18	0.5	0.5	0.6	2.9
		4	180	3	0	80	6	0.1	0	1.4	4.1
	Normal fasting values			35-110	4.0-20.0	25-80	10-60	0.3-2.0	0.4-2.2	3.0-10.0	1.0-5.0

*Amylase absent before 6 mo. of age.
†Range of values before & after cortisone.
‡Stimulation from observing food.
§Specimen not analyzed.

The mother of the child with pancreatic fibrosis (Case 7) had low fasting procarboxypeptidase, carboxypeptidase and lipase levels. With the pronounced stimulation of bile flow after cortisone administration procarboxypeptidase and carboxypeptidase rose, but no effect on lipase was observed. The child with rheumatic fever (Case 10), who had low amylase and protease values initially, exhibited a slight increase after observing food, but reached normal values at the time of maximum choleresis with cortisone. The infant suspected of having pancreatic insufficiency (Case 13), who had low fasting values, had a rise in tryptic and carboxypeptidase activities to within normal range after cortisone administration; there was a slight increase in lipase activity. These changes after cortisone suggested adequate pancreatic reserve. Both the adult with chronic pancreatitis (Case 8) and the infant with pancreatic fibrosis (Table 3, Case 15) had practically no pancreatic enzymes in the fasting state. There was no change in enzyme measurements in the adult after cortisone. In the infant trypsin was the only enzyme measured after cortisone, and no activity was demonstrable.

It should be noted that, in these studies, the pancreatic-enzyme activity of the duodenal fluid was measured in terms of concentration only. A much greater output of pancreatic enzymes than is apparent from the recorded results probably followed cortisone administration, since the increase in bile flow also observed would dilute the pancreatic secretion and decrease the enzyme concentration of the duodenal fluid.

The pH of the fluid remained alkaline, and no significant change in chloride concentration followed cortisone administration in any patient studied. This indicates that the increase in volume was not due to a significant stimulation of gastric secretion.

Discussion

Both intravenously administered and duodenally instilled cortisone produced a consistent rise in the bilirubin concentration of the aspirated duodenal contents. This frequently preceded the increase in volume observed. In most cases an increase in total bilirubin secretion also followed intravenous administration of cortisone.

Sodium dehydrocholic acid (Decholin) is one of the few intravenous therapeutic agents previously known to increase the flow of bile from the liver. This drug increases the volume flow (hydrocholeresis) but does not substantially increase the elaboration of bile pigments or bile salts (choleresis). In contrast cortisone appears to have not only a hydrocholeretic but also a true choleretic action. In addition, cortisone has a more prolonged action than Decholin, which causes stimulation lasting only thirty to forty-five minutes, whereas the effect of cortisone persists for several hours. The increase in volume and bilirubin content that occurred within thirty minutes of administration was probably due to an immediate, direct action of cortisone on the biliary secretory mechanism of the liver. The greater increase in these constituents observed three or four hours later indicated a delayed effect of the hormone that may have been related to bile-salt synthesis. The increase in bile flow apparently was not due solely to gall-bladder contraction since similar responses were observed in patients lacking gall-bladder function.

This choleretic action of cortisone may, in part, explain the decrease in serum bilirubin levels and in icterus that occurs in patients with liver disease who have been treated with cortisone or ACTH. Cortisone itself, or the cortisone-like steroids produced by ACTH stimulation of adrenal secretion, may increase the biliary-tract flow of bile and thereby induce a "filtering off" of the excess bile retained in the patient's serum. The choleresis observed with cortisone resembles the effect of sodium dehydrocholic acid and ketocholanic acids (bile salts) on infants with icterus due to biliary insufficiency, or with inspissated bile secondary to hepatitis, since it has been shown that these agents relieve intrahepatic obstruction, reduce jaundice and lower serum bilirubin levels.[20]

In addition to its choleretic effect cortisone may facilitate bile flow by diminishing inflammation and edema about the smaller bile canaliculi in the diseased liver. The prompt response to cortisone in these studies suggests that the choleretic action is probably of greater importance, since an anti-inflammatory action probably would not occur so quickly.

The additional observation of increased pancreatic-enzyme activity of the duodenal fluid in patients with low initial values, which were presumably not due to actual pancreatic destruction, may be caused either by a pancreozymic-like action of cortisone on the pancreas or by the unexplained potentiating action of bile on pancreatic secretion resulting from the choleretic stimulus of the cortisone. The same phenomenon has been observed with the use of bile salts to relieve biliary obstruction in hepatitis of infancy.[20,21] This response to cortisone suggests its possible use as a stimulus to pancreatic secretion in patients suspected of having pancreatic insufficiency.

The results of this study indicate that cortisone has a choleretic action on the liver that results in an increase in bile content and in pancreatic enzyme activity of the duodenal fluid, and should assist in greater alimentary digestion in the same manner as the increased gastric secretion produced by cortisone does.[22] This effect may also explain the striking improvement in fat digestion and absorption noted in patients with steatorrhea during cortisone therapy.[23]

Summary and Conclusions

Cortisone has been shown to possess hydrocholeretic and choleretic actions both in normal subjects

and in patients with various alimentary tract disorders. These effects may explain the decrease in serum bilirubin levels observed during cortisone or ACTH therapy of patients with hepatitis and other diseases of the liver.

Cortisone did not produce an increase in pancreatic enzyme activity in the duodenal fluid of subjects with achylia due to pancreatic destruction. In 2 subjects with reduced fasting values, however, cortisone administration was accompanied by an increase in enzyme activity of the duodenal fluid, suggesting adequate pancreatic reserve.

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A STUDY OF ILLNESS IN A GROUP OF CLEVELAND FAMILIES*

VI. Controlled Study of Reactions to Oxytetracycline Hydrochloride

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A CONTROLLED study was recently undertaken to evaluate the effect of relatively small, daily doses of an antibiotic, oxytetracycline hydrochloride,** in the prevention and treatment of common upper respiratory illnesses in a group of Cleveland families.[1] The small doses used were associated with an unexpectedly large number of reactions, requiring discontinuance of the study after a week. It is the purpose of this paper to report the frequency and nature of these reactions, as determined by comparison of the occurrence of symptoms in the experimental and control groups.

Methods

The general methods used in the study of this group of families have been described elsewhere.[1] Families volunteered for the present study with the approval of their personal physicians. Subjects were separated into drug and placebo groups on the basis of random selection, and all members of a family received the same type of medication. One week's supply of oxytetracycline hydrochloride or placebo†† was distributed in separate containers to each person. To maintain complete objectivity neither the subjects, the examining physicians, nor the visiting field workers were informed which containers had oxytetracycline hydrochloride and which had placebo. Both the drug and the placebo were administered as a liquid suspension to children and as capsules to adults. Children twelve years of age or older received capsules, as did younger children on

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**Oxytetracycline hydrochloride (Terramycin) and placebo kindly supplied by Charles Pfizer and Company, Incorporated, Brooklyn, New York.

††Placebo capsules contained cornstarch and yellow dye No. 4, and the placebo suspension contained sucrose, sodium sucaryl, kelcosol, red dye No. 2 and imitation raspberry flavoring.

request. The dose of oxytetracycline hydrochloride was 250 mg. twice daily for children one to eleven years of age and 500 mg. twice daily for persons twelve years of age or older. Comparable volumes of placebo were given.

The usual methods of observation[1] were continued, including weekly visits by field workers, illness calls by physicians and daily recording of symptoms by mothers. Within a week of discontinuation of the medication the field workers visited the families with history sheets designed to elicit detailed information concerning reactions in each subject. The field workers filled out these sheets with the aid of the mothers and the daily symptom records. The day of occurrence, duration and severity of each symptom were indicated. Three degrees of severity were recorded as follows: "mild," a symptom that required no change in the routine daily activities of the subject and resulted in no inconvenience; "moderate," one that resulted in inconvenience but did not necessitate discontinuance of the medication; and "severe," one that resulted in extreme inconvenience or necessitated discontinuation of the medication. The number of doses of medication ingested were also recorded on each chart. The charts were then checked against the daily records of symptoms kept by the mothers, and results were coded by a physician who was unaware of the identity of the subjects in the placebo and drug groups.

Symptoms that occurred during the study were classified as gastrointestinal, respiratory, nonspecific and miscellaneous. Gastrointestinal symptoms included anorexia, nausea, vomiting, abdominal pain, abdominal cramps, diarrhea, loose stools, rectal pain, rectal burning, rectal itching, abdominal "gas," abdominal "distress," abdominal "rumbling," hunger for salty foods and pain or burning of mouth or tongue. Respiratory symptoms consisted of sneezing, nasal discharge, nasal obstruction, sore throat, hoarseness, cough, sputum production, wheezing, pain or pressure in ear or sinus and nonrespiratory symptoms associated with one or more respiratory symptoms—for example, cracked lips, burning or itching eyes and cold sores. Nonspecific symptoms comprised fever, headache, dizziness, muscle aches, weakness, malaise, listlessness, fatigue, chilliness, feverishness and diaphoresis. Miscellaneous symptoms included pain or burning on urination, vaginal itching and burning, "hot flush with perspiration" and rash or skin eruption (excluding cold sores). In certain cases "sore eyes," burning eyes, puffy eyelids, difficulty in focusing and cracked lips were not associated with the presence of respiratory symptoms and were considered as miscellaneous symptoms.

A diagnosis of illness was made when possible. Such illnesses included common cold, pharyngitis, sinusitis, otitis media, otitis externa, hay fever, bronchial asthma and conjunctivitis and, in the placebo group, nonbacterial gastroenteritis. Only 2 cases of gastroenteritis occurred in the placebo group: in the drug group this diagnosis could not be made because of the nature of the reactions.

Comparison of Drug and Treated Groups

There were 101 persons in 20 families who received oxytetracycline hydrochloride, and 86 persons in 18 families who received placebo. The median number of persons per family in each group was 5. Of children between the ages of one and eleven years inclusive, there were 56 in the treated group and 45 in the control group; in these two groups the age distributions were similar. Each group had a total of 5 children who were twelve years of age or older.

TABLE 1. *Occurrence of Symptoms during the Period of Medication with Oxytetracycline Hydrochloride or Placebo.*

Class of Symptoms	No. of Persons		Percentages of Persons	
	Drug Group*	Placebo Group†	Drug Group*	Placebo Group†
Gastrointestinal	72	22	71	26
Respiratory	11‡	14‡	12‡	18‡
Nonspecific	19	15	19	17
Miscellaneous	12	5	12	6

*101 persons.
† 86 persons.
‡Occurrence of respiratory symptoms based on 91 & 76 persons in drug & placebo groups, respectively, since respiratory symptoms observed in remainder had started before period of medication.

The modal duration of medication in each group was seven and a half days, and the 90 percentile range was six and a half to eight and a half days. In the drug and placebo groups the modal daily dose was 0.5 gm. in children eleven years of age or younger and 1.0 gm. in persons twelve years of age or older, whereas the modal total dose was 3.75 and 7.5 gm. The 90 percentile daily dose was within 0.1 gm. of the modal daily dose. This analysis indicates that the two groups were comparable for purposes of the study and in relation to the conclusions drawn.

Results

During the period of drug administration 71 per cent of the persons in the drug group and 26 per cent of those in the control or placebo group noted the onset of one or more gastrointestinal symptoms (Table 1). Differences in the numbers of persons who manifested other symptoms during this interval were smaller, but some of these differences were significant, as indicated below.

In many cases the duration of symptoms continued beyond the period of drug administration, and symptoms occasionally appeared after discontinuation of the medication. For example, in certain persons with prolonged episodes of loose stools or diarrhea, pain or burning of the rectum developed after the drug was discontinued. To evaluate such delayed symptoms a comparison was made between the numbers of persons

who had new symptoms during approximately seven and a half days of medication and during the subsequent week (Table 2). Additional gastrointestinal symptoms rarely appeared later than seven days after the discontinuation of medication. During this interval a striking reduction occurred in the prevalence of numbers of persons with nonspecific symptoms were compared, were not noted in persons with respiratory symptoms. In the placebo group the longest duration of gastrointestinal symptoms was nine days. In the drug group 29 per cent of the persons had symptoms lasting longer than nine days, the longest duration being thirty-nine days. The great variety and small number of miscellaneous symptoms did not permit comparison as a class of symptoms.

TABLE 2. *Occurrence of Symptoms during the Period of Medication with Oxytetracycline Hydrochloride or Placebo and during the Subsequent Seven Days.*

Class of Symptoms	Percentage during Interval of Medication*		Percentage during Subsequent Seven Days	
	Drug Group†	Placebo Group‡	Drug Group†	Placebo Group‡
Gastrointestinal	71	26	4	6
Respiratory	12§	18§	14§	17§
Nonspecific	19	17	11	6
Miscellaneous	12	6	4	0

*About 7.5 days.
†101 persons.
‡86 persons.
§Occurrence of respiratory symptoms based on 91 & 76 persons in drug and placebo groups, respectively, since respiratory symptoms observed in remainder had started before period of medication.

The average number and duration of gastrointestinal and nonspecific symptoms were compared (Table 4). This analysis showed that when gastrointestinal symptoms appeared the type of gastrointestinal reactions differed in that they were characteristically more numerous, and more prolonged in the drug than in the control group. The average number and duration of nonspecific symptoms per case were similar in the two groups. About 50 per cent of persons with gastrointestinal symptoms in the drug group had noted the onset of these symptoms by the second day after starting medication, and 75 per cent by the fourth day (Fig. 1). The corresponding 50 per cent level in control persons was the fourth day, whereas the 75 per cent level was the sixth day. The occurrence of loose stools or diarrhea, the predominating gastrointestinal symptom, followed the same pattern (Fig. 1).

TABLE 3. *Occurrence of Multiple Symptoms, Severe Symptoms and Symptoms Lasting One Week or Longer in Persons Receiving Oxytetracycline Hydrochloride or Placebo.*

Class of Symptoms	Percentage with Two or More Symptoms		Percentage with Severe Symptoms		Percentage with Symptoms Lasting One Week or Longer	
	Drug Group*	Placebo Group†	Drug Group*	Placebo Group†	Drug Group*	Placebo Group†
Gastrointestinal	50	14	26	5	41	3
Nonspecific	27	19	7‡	1	5	3

*101 persons.
†86 persons.
‡Based on 94 persons in group since information concerning severity inadequate in 7 persons.

new onsets of gastrointestinal symptoms in the drug group, whereas the frequency of new respiratory symptoms remained essentially the same. There was a definite, but less marked, decline in the number of onsets of nonspecific and miscellaneous symptoms. In the control group, some decrease was noted in the onsets of all symptoms except the respiratory. The frequency of new gastrointestinal and respiratory symptoms was approximately the same in both groups during this period.

A comparison was made, in the drug and placebo groups, of the percentage of persons who had two or more gastrointestinal or nonspecific symptoms, the percentage who experienced severe symptoms and the percentage who had symptoms lasting longer than a week (Table 3). Multiple gastrointestinal symptoms occurred more frequently in members of the drug than in those of the placebo group (ratio of 3.7 to 1), and a greater percentage of the former had symptoms of increased severity (ratio of 5.2 to 1) and symptoms of longer duration (ratio of 14 to 1). These differences, which were apparent to a lesser degree when

TABLE 4. *Average Number and Duration of Gastrointestinal and Nonspecific Symptoms in Persons Receiving Oxytetracycline Hydrochloride or Placebo.*

Symptom	Average No. of Symptoms per Case		Average Duration* per Case	
	Drug Group	Placebo Group	Drug Group	Placebo Group
			days	*days*
Gastrointestinal†	2.5	1.6	8	4
Nonspecific‡	2.3	2.2	3	3

*Corrected to nearest day.
†Averages for gastrointestinal symptoms based on 76 cases in drug & 27 cases in placebo group.
‡Averages for nonspecific symptoms based on 30 cases in drug & 20 cases in placebo group.

The frequency of the individual gastrointestinal and nonspecific symptoms was compared in the drug and control groups (Table 5). The most common complaint—that of loose stools or diarrhea—was present

in 69 per cent of the drug and 16 per cent of the control group. More than 90 per cent of persons with gastrointestinal symptoms in the oxytetracycline group had loose stools or diarrhea, whereas approximately half the control subjects with gastrointestinal symptoms experienced this symptom. About a third of those in the drug group had abdominal pain or cramps, the next most common symptom. The remaining complaints, in decreasing order of frequency, were rectal burning or itching or pain, anorexia, "gas" or "rumbling" or abdominal "distress," nausea, vomiting, pain or burning of mouth or tongue and hunger for salty foods. All these symptoms occurred more often in the drug than in the placebo group, and this difference was even more evident when the comparison was limited to severe symptoms.

Weakness, malaise, listlessness or fatigue was a complaint in 21 per cent of the persons receiving the drug and in 10 per cent of the control subjects, and dizziness was noted by 6 and 2 per cent of these groups, respectively. The frequency of fever, headache, muscle aches, chilliness, feverishness and diaphoresis was similar in the drug and control groups. When comparison was limited to severe symptoms, however,

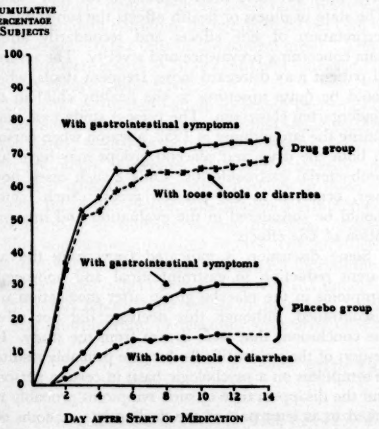

FIGURE 1. *Cumulative Occurrence of Gastrointestinal Symptoms after the Administration of Oxytetracycline Hydrochloride or Placebo.*

headache, muscle aches and weakness were definitely more frequent in the treated group.

Among the miscellaneous symptoms in the drug group were 7 cases of pain or burning during urination and 1 of vaginal itching and burning. In addition 3 persons in the drug group had burning or "sore" eyes with either puffy eyelids or difficulty in focusing, without symptoms of respiratory disease, and 2 in the drug group had cheilosis without respiratory disease. None of these miscellaneous symptoms were present in the control group. Three persons in the drug group had fine, morbilliform rashes on the chest or back, and none of the controls had such lesions. Three of the control group and one of the drug group had "dry rash" or "eczema" of the face. Isolated single miscellaneous diagnoses included external otitis and conjunctivitis in the drug group and pimples behind the ears, "hot flush" and roseola in the control group.

TABLE 5. *Occurrence of Individual Gastrointestinal and Nonspecific Symptoms in Persons Receiving Oxytetracycline Hydrochloride or Placebo.*

Symptom	Total Occurrence		Occurrence of Severe Symptoms	
	Drug Group	Placebo Group	Drug Group	Placebo Group
	%	%	%	%
Gastrointestinal:				
Loose stools or diarrhea	69	16	18	3
Abdominal pain or cramps	31	10	8	1
Rectal pain, itching or burning	27	3	8	0
Anorexia	22	9	5	0
"Gas," "rumbling" or "distress"	18	2	3	0
Nausea	14	6	5	1
Vomiting	4	0	2	0
Other*	3	1	1	0
Nonspecific:				
Weakness†	21	10	5‡	1
Headache	14	16	4‡	1
Chilliness, feverishness & diaphoresis	12	7	0‡	0
Muscle aches	10	9	5‡	0
Dizziness	6	2	1‡	0
Fever	6	7	0‡§	1§

*Hunger for salty foods, pain or burning of mouth or tongue.
†Includes also malaise, listlessness & fatigue.
‡Based on 94 persons in group since information concerning severity inadequate in 7 persons.
§Temperature of 103°F. or higher.

Discussion

Oxytetracycline hydrochloride was introduced as a new antibiotic in 1950.[2] Within a few months the first of a continuing series of reports of toxic and side effects appeared in the medical literature.[3,4] It has been generally agreed that gastrointestinal symptoms predominate, but there have been differences in the frequency and severity of symptoms observed. One early study[5] reported that medication had to be discontinued in only 1 of 108 cases of infection in which adults received 4 gm. daily and children correspondingly less, according to weight. This report further stated, "Toxic reactions, consisting of nausea, vomiting, and loose stools, were uncommon." In another study[6] 70 tuberculous patients received 5 gm. of the drug daily for a hundred and twenty days, and in none

was it necessary to discontinue the medication. Anorexia and frequent, loose stools were observed in 70 per cent of these patients, whereas nausea and vomiting occurred in 50 and 13 per cent, respectively. Although these investigators[6] believed that the loose, frequent stools could "hardly be regarded as a toxic manifestation, since it was not troublesome or annoying to the patient" others[7] have described severe vomiting and diarrhea, which necessitated the discontinuation of medication in 10 per cent of 93 patients who had received 3 to 5 gm. daily. In addition the drug was discontinued because of reactions in 13 per cent of 87 patients in one series[8] and in 14.7 per cent of 143 patients in another.[9] An anorectal syndrome has been described[10] that consists of rectal pain, itching or burning occurring after the onset of loose stools or diarrhea and persisting for periods as long as several weeks. Severe diarrhea was noted in 18 per cent of the drug group in the present series, and the anorectal syndrome occurred in 27 per cent and resulted in complaints of extreme inconvenience or in discontinuation of medication in 8 per cent of the persons receiving oxytetracycline hydrochloride.

The clinical reactions to oxytetracycline hydrochloride can be divided into three principal classifications—namely, primary irritative effects on the gastrointestinal tract, effects secondary to alteration of bacterial flora and allergic effects. Such a grouping helps clarify some of the reported differences in prevalence, severity and interpretation. The main irritative effects are anorexia, nausea and vomiting. The frequency and severity of this group of symptoms, though appreciable, was lower in the present study than in others.[6,9,11-15] This is readily explained by the smaller doses administered in the present study. A similar result was observed in another series of patients who received small amounts of the drug.[10] That series was not strictly comparable to the present one, however, since medication was administered in the form of troches, and the irritative substance was thus kept in the mouth until dissolved.

Daily ingestion of 2 to 4 gm. of oxytetracycline hydrochloride results in a reduced bacterial count of intestinal flora within about forty-eight hours[16] and "virtual elimination of normal aerobic flora."[15] Resistant yeasts, candida and micrococci persist.[17,18] This alteration of flora is the probable basis for the appearance of loose, frequent stools or diarrhea noted in 69 per cent of the subjects receiving the drug in the present series. Secondary complaints of rectal pain, rectal itching, rectal burning, abdominal "distress," abdominal pain, abdominal cramps, "gas" and "rumbling" were common. Such manifestations as cheilosis, glossitis, stomatitis, pharyngitis, pharyngeal ulceration, vaginal pruritus and pain or burning on urination have also been associated with alteration of flora by the drug.[9,10,19,20] Apparently, the amount of oxytetracycline hydrochloride that causes alteration of bacterial flora is smaller than the amount that usually causes gastrointestinal irritation. This is probably the reason for the lower frequency of irritative effects and the high prevalence of loose stools in the present study, as contrasted to previous studies in which larger doses of drug were administered.

The morbilliform rashes observed in the present series were probably examples of the allergic effect of oxytetracycline hydrochloride. In this study allergic phenomena were infrequent and not severe. In other studies, however, severe reactions necessitating discontinuation of medication have been reported—for example, cases of erythema, pruritus, urticaria and bullae (patient also allergic to chlortetracycline),[21] pruritic urticaria[22] and dyspnea, edema, reversal of albumin-globulin ratio, proteinuria and hematuria.[23]

Additional factors that should be considered in the evaluation of reported differences in severity, prevalence and interpretation of side effects are the presence or absence of control groups and the state of illness or health of the subjects. Almost all previous studies lacked controls; thus the reported occurrence of side effects is inaccurate. Side effects in sick patients may have been considered part of the disease by the patient or the observing physician, and discontinuation of the drug may not have been considered for that reason. The state of illness or health affects the subjective interpretation of side effects and secondarily affects data concerning prevalence and severity. The severely ill patient may disregard loose, frequent stools, which could be quite upsetting to the healthy child in the kindergarten classroom. The present study took place during the late summer of 1953, a season when persons in both the drug and placebo groups may have had nonbacterial gastroenteritis. Only 2 such cases, however, occurred in the placebo group. Such factors should be considered in the evaluation and interpretation of side effects.

Some discussion is indicated concerning the apparent reduction in gastrointestinal and nonspecific symptoms in the placebo group after medication was discontinued, although this decrease did not affect the conclusions that were drawn from the study. Ingestion of the unidentified substance probably resulted in symptoms on a psychologic basis in certain persons, and the disappearance of such symptoms probably resulted in at least part of the decline in symptoms observed in the placebo group. In addition it should be noted that, as a result of the large number of persons who manifested gastrointestinal symptoms during the first week (Table 2), the number of subjects in whom such symptoms could have developed during the second week was decreased, and the number in whom new symptoms occurred was necessarily smaller. Percentage occurrences during the second week would thus have been greater if calculated on the basis of the potential development of symptoms.

The families in the present study were volunteers from a healthy population. They were selected solely on the basis of their willingness to participate in a

study that they were informed would continue for six weeks. Despite their state of health and willingness 11 subjects, or 11 per cent, in the drug group found it necessary to discontinue the medication because of symptoms, and others were contemplating discontinuing the drug if their symptoms continued. The original purpose of the study had been to evaluate the effect of a daily dose of oxytetracycline hydrochloride in the prevention and treatment of common upper respiratory illnesses. Because of the high frequency of severe reactions the problem as outlined by the original purpose could not be solved. Data concerning the prevalence of reactions to other antibiotics under comparable circumstances are not available. Such studies would be highly desirable.

Summary

In a group of 20 Cleveland families 101 adults and children were given 1.0 and 0.5 gm. respectively, of oxytetracycline hydrochloride (Terramycin) each day for seven and a half days. Corresponding amounts of placebo were administered to 86 other members of 18 families. The relatively small doses resulted in a high prevalence of reactions, primarily gastrointestinal, in the drug group. Loose, frequent stools or diarrhea was the predominant symptom, occurring in 69 per cent of the drug and 16 per cent of the control group. These symptoms were severe in 18 per cent and 3 per cent of the two groups, respectively.

The drug group also had an increased frequency of certain nonspecific symptoms, including weakness, dizziness, severe headache and severe muscle aches. Multiple symptoms, symptoms of increased severity and prolonged symptoms were more frequent in those receiving the drug; certain miscellaneous symptoms—that is, pain or burning during urination, vaginal itching and burning, burning of eyes with puffy eyelids, difficulty in focusing, cheilosis and morbilliform rash—occurred only in persons who received the drug.

Previously reported differences in prevalence, severity and interpretation of reactions were attributed to lack of controls, inaccuracy of evaluating side effects in the presence of disease (especially severe disease) and the error of discussing all side effects together despite probable differences in the basic mechanisms of such reactions.

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SPECIAL ARTICLE

INTEGRATING PREVENTIVE AND SOCIAL MEDICINE IN THE MEDICAL CURRICULUM*

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PHILADELPHIA

BEFORE one can talk intelligently about integrating preventive and social medicine in the medical curriculum, the meaning of these much-used and often abused terms must be clarified.

Definitions

The prevention of specific disease may be said to have begun in England in 1796, when Jenner demonstrated that cowpox confers an immunity that protects against smallpox. In this early beginning it is noteworthy that sound scientific principles were applied to disease prevention. Jenner said, "I placed

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it upon a rock where I knew it would be immovable before I invited the public to take a look at it." Not always has a similar solid foundation been apparent in some of the more recent ventures in preventive medicine.

Ever since the days of Jenner, preventive medicine has had a clear meaning in its specific sense. One prevents smallpox, diphtheria, typhoid fever, rabies, tetanus and many other diseases through the use of specific immunizing agents and through the application of well established hygienic measures. Confusion arises, however, when the term, preventive medicine, is used more broadly. On the one hand it may be thought of as interchangeable with public health. On the other, preventive medicine may be so interwoven into the whole fabric of medicine that it loses its own identity and one hears it said, "preventive medicine is medicine."

If the meaning of preventive medicine is confused, that of social medicine is even more so. In the attack on venereal disease social medicine came to mean syphilis and gonorrhea. More recently, in the all-out war between organized medicine and the Truman administration over the issue of a national system of compulsory health insurance, socialized medicine was held up before the American public as a threatening evil. The average citizen — and many a physician too — does not really know what he means by socialized medicine but he is sure that it is bad. And social medicine does not sound very different.

There is not a chair of social medicine in any medical school in the United States. One school of public health has had the courage to designate a department of social medicine as a field for postgraduate study. In the medical schools, however, the term has been avoided. For the most part medical-school departments are called public health and preventive medicine or perhaps just preventive medicine, the term being applied in its general meaning. Occasionally, one finds a department of community health or a department of environmental medicine.

For a definition of social medicine I therefore turn to the well established use of the term in Great Britain and Western Europe and quote a statement made by the late Dr. John Ryle,[1] who became the first professor of social medicine at Oxford in 1943. His opening words have a delightful Alice-in-Wonderland appeal:

> Social medicine means what it says. It embodies the idea of medicine applied to the service of man as *socius*, a fellow or comrade, with a view to a better understanding and a more durable assistance of all his main and contributory troubles which are inimicable to active health, and not merely to removing or alleviating a present pathology. It embodies also the idea of medicine applied in the service of *societas*, or the community of men, with a view to lowering the incidence of all preventable disease and raising the general level of man's fitness.[1]

Professor René Sand[2] views the matter in historic perspective and describes social medicine as the ultimate in man's quest for more abundant health:

> Social medicine is the final flowering of the preventive and curative art. It satisfies at once man's material interest, his reason, his sense of communal responsibility and that unconquerable aspiration toward a better life on which his hopes are nourished. . . .
>
> In that it has always existed under one form or another, social medicine is a heritage of the past. It is the result of the adaptation of medicine to the needs of the times before the inescapable compulsion of those scientific, economic, and moral forces which shape the ends of society.

In the light of such an interpretation of social medicine the meaning of preventive medicine that is gaining popularity in the United States today merits consideration. As defined recently by Leavell and Clark,[3] "Preventive medicine is the science and art of preventing disease, prolonging life, and promoting physical and mental health and efficiency." This definition includes preventive medicine as practiced either by the private practitioner dealing with his individual patients or the public-health officer with aggregations of individuals in his community. Public health is then looked upon as a division of preventive medicine — a part that requires organized community effort or action.

In this broad sense there is little difference between the meaning of preventive medicine in the United States and the meaning of social medicine, which is the term more generally used throughout Western Europe. Each recognizes the relation between man and his environment; each implies the importance of social factors as they influence health.

The scope of preventive medicine has been further clarified by Leavell and Clark[3] in a concept based on five levels at which principles of prevention may be applied on either an individual or a community basis: health promotion; specific protection; early recognition and prompt treatment; disability limitation; rehabilitation. At these various levels measures may be applied to the agent, the host or the environment.

Health promotion is used in a positive sense in that certain procedures may be employed to promote a state of general well-being of high degree rather than being directed at any particular disease or disorder. Health education is included under this heading whether for the group or for the individual. Also in this category would be placed such general health measures as adequate nutrition, proper housing and favorable environmental conditions in the home and in occupational employment.

Specific protection represents prevention in its strictest sense. Here measures are taken against a particular disease or group of diseases to intercept their causes before they involve man. Some measures may be applied to the environment, as when a sewage-disposal plant is installed in a town. Others may be applied directly to man himself — for example, immunization procedures.

Early recognition and prompt treatment is a level of prevention that has long been recognized in the control of disease, whether approached on a mass or an individual basis. Measures are taken to prevent spread of disease to others if the disease is a communicable one, to cure or arrest the pathologic process, to prevent complications and to shorten the period of disability. This level applies particularly to disorders for which there are no specific preventive measures — for example, cancer and diabetes.

Disability limitation implies the prevention or delaying of the consequences of clinically advanced or nonpreventable or noncurable disease. Here treatment of the pathologic process, even when it is firmly established, may still prevent its continued course and prevent defect or disability and postpone death.

Rehabilitation is the fifth level, which, although at the far end of the spectrum, is today being given increasing attention as an important part of the broad field of prevention. Although disease may have permanently handicapped the patient and changes in form and function are no longer reversible measures may be taken both to help the patient and to modify his environment so that he may return as a useful member of society.

Quite obviously, if one accepts preventive medicine from this fivefold point of view, it cannot be taught to students exclusively by teachers in any one department. It calls for integrated teaching involving virtually all medical-school departments. Preventive medicine, then, becomes not so much a separate and distinct discipline as an attitude that permeates the entire medical curriculum.

The significance of this attitude and the ways in which it can be developed in the student were the subject of an intensive five-day conference under the heading "Preventive Medicine in Medical Schools" held at Colorado Springs in the fall of 1952. No one who attended that conference or who reviewed it in the written report[4,5] could help being impressed with the number and variety of methods currently being used to integrate preventive medicine into the medical-school curriculum. Some of these appear to be well established; others are frankly new and experimental. Some of the more important trends may be drawn together into two broad categories: those described under the heading of human ecology, and those emphasizing the teaching of health as distinguished from the teaching of disease.

Human Ecology

Common to a number of present teaching methods is the objective to bring the student into responsible relation with the patient and his family in the home and in the community. The home and the community then become the laboratory for learning and for scientific investigation. Direct observation and participation are as important here as in the dissecting room or the physiology laboratory or at the bedside. It follows, therefore, that the student must actually get out into the community to appreciate the factors in the family and in the home that may have an important bearing upon health and illness.

Many medical schools have devised ways of providing students with varying degrees of experience with the family in its own home. For the most part this experience has been in the third or fourth year of medical school along with clinical training. More recently, however, students have been brought into contact with families earlier in the curriculum, even at the beginning of the first year.

As an example of a plan that gives the student an opportunity for continuous contact with the same family throughout the four years of the medical curriculum mention may be made of the so-called Family Health Advisor Service at the University of Pennsylvania School of Medicine.

Family Health Advisor Service

Preliminary reports have described the experience of the first exploratory years in this new teaching method.[6,7] Now, four years after its introduction, the freshman students who first entered the program as an elective course in the fall of 1949 have reached graduation, and from each succeeding class more students have been included in the group. As students and faculty together have explored this experiment in learning, its value has become clearer, and its position in the medical curriculum more firmly established.

The families are selected with considerable care by the Social Service Department of the University Hospital. The criteria for selection are few and flexible. The families live conveniently close to the hospital so that student travel time is kept to a minimum. Most of these families look to the hospital for their medical care; only a few have private family physicians. The social and economic status of the families varies, from those who are self-supporting to those who are on relief.

The students visit their assigned families about once a month and more often when indicated for some special problem or illness. They do not make diagnoses or prescribe treatment, for which they are not prepared and which is not the purpose of the program; plenty of such experience is available to them elsewhere in the medical curriculum. Their function is to advise the family and help it meet its medical and related needs. They learn how a hospital clinic works as they help some member of the family with a clinical appointment; through familiarity with the home and the social background they are often in a position to interpret a situation or a symptom to the clinic physician or to interpret the physician's instructions to the patient. As they con-

tinue with these families during the course of the four years they assume gradually increasing responsibility in a physician-patient relation that is very real because they are active participants, not mere observers.

Each student in this elective course has close faculty supervision. Members of the departments of preventive medicine, medicine, psychiatry, pediatrics, surgery and social service co-operate in the program. For teaching purposes the students are divided into groups of 8. Each group meets regularly with a team of 3 instructors: 2 clinicians, 1 of whom is a psychiatrist, and a social worker.

Reports submitted by students at the end of each year, interviews with students and impressions of the faculty all bear witness to the values in this learning experience. Early in the course of events various members of the faculty team listened with surprised gratification when first-year and second-year students began saying, "What we have learned in this experience is that we must consider the patient as a whole, rather than just his disease, and we must also consider the influences of his family and environment that affect his well-being."

The family in its own home has a training potential of special importance in the teaching of preventive medicine, for here the student has the opportunity to look at health rather than disease — to look at the positive side of the ledger. In the normal course of events, a medical student sees people who are already patients; something has gone wrong and the patient seeks medical attention to help set matters right. On the other hand, when a student assumes responsibility for the health of a family, — especially when this responsibility is continuous over his four years of medical school, — he learns to think in terms of what may be done to keep these people from becoming patients. In the home the student has an opportunity not only to observe but also to participate in an active program of health maintenance for the family: health supervision for the infants and pre-school children, follow-up study of school health programs, the nutritional status of the family, the emotional tensions of intrafamilial relations, the detection and management of chronic disease and the problems of the aged. Also, he becomes familiar with community health agencies that in one way or another may touch upon the health needs of his assigned family. By means of visits to health centers, well-baby clinics, school health centers, rehabilitation agencies, occupational health programs and many other services, the student comes in direct and personal contact with community health resources.

This type of family health service should be distinguished from other home-care programs in which the student visits a family only when called upon for purposes of diagnosis and therapy. In such programs the students are generally "on service" for a limited period of a few weeks or a few months. They may visit a particular home only once or twice for a specific problem, which may be an inflamed eardrum or an abnormal blood count. Differential diagnosis, patient management and specific treatment may be discussed in the light of social and environmental circumstances in which the patient is seen, but the primary attention is given to the details of medical care.

A program in which the chief emphasis is on treatment has an inherent danger. There is a temptation to use the student's time to meet a demand for medical attention for those who cannot afford private care. Expediency may outweigh educational value. In any event a home-care program designed primarily for definitive treatment of specific episodes should be distinguished from that described above, in which the primary emphasis is graduated responsibility for family health as well as illness. When treatment is the primary purpose of a visit, the situation is really a home sample of what has been aptly called "episodic medicine." In contrast, a periodic home visit may have no episode to precipitate the call. The student visits the family at his and their convenience for the purpose of observing home environment and evaluating the family's health status. The student's responsibility for the family and its complexity of medical needs does not end with the visit but continues from month to month, as that of the family physician does. Only as a doctor or the medical student has time, on repeated visits, to gain the confidence of all members of the family and to seek beyond the obvious will it be possible for him to deal with all the factors involved in promoting the health of the family unit.

Teaching Health

A second general trend in the teaching of preventive medicine is seen in a shift from teaching disease to teaching health.

But how does one teach health? It is a difficult task and one with which medical faculties are far less familiar than the teaching of disease. Disease can be demonstrated. The student can see what causes it and what it does to the tissues of the body. If it is a case of pneumonia, he can see the pneumococcus in the microscope and on a culture plate. He can see the pathological changes in the lungs and observe the effects of therapy. But how does one demonstrate health? What does one hold up before the student to say to him, this is health, measure it, test it and see what it does?

Too often the student comes to look upon health as what it is not. If his patient, after thorough examination does not have any detectable evidence of disease, the student calls him healthy.

This problem does not appear to be confined to the United States. Dr. Richard Scott,[8] of the University of Edinburgh, in outlining the background

and objectives of a teaching program that has much in common with the family health studies described above, states:

> The basic training of doctors and (perhaps to a lesser extent) of almoners has conditioned them to think of health, if indeed they think of it at all, as merely the absence of disease. It leaves them apparently ill-equipped to set out on a serious study of the positive attributes of health.

The World Health Organization has endeavored to establish a more positive understanding of health in its now familiar definition: "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." But to convince the student of this positive concept and to make him really believe that health is something more than a vacuum in which disease does not exist requires the application of the same principles of observation and participation that he has found convincing in the study of pathology and therapy.

Three fields in particular are available to demonstrate to the student that health is a positive reality with measurable attributes and demonstrable cause and effect: pediatrics, occupational health and military medicine.

Pediatrics

Pediatrics, perhaps more than any other field of medicine, actually practices health maintenance. A recent national survey of child-health services showed that 54 per cent of a pediatrician's visits on an average day were for health supervision of well children; less than half his day's visits were for the care of sick children. Of the services given by the general practitioner to children approximately a third were for the supervision of their health.[9]

The increasing attention given to health maintenance in the practice of both pediatricians and general practitioners has not been altogether by design; it came about inevitably as the communicable diseases of childhood were brought under control, as rickets and scurvy were virtually eliminated and as infant nutrition became greatly simplified. But. however it has happened, one talks today more of child health and less of the diseases of children. In Britain chairs of child health have been established. Although in the United States medical schools still cling to chairs of pediatrics there is one medical-school department of child health, and departments of maternal and child health are included in the graduate schools of public health.

In recognition of the change in pediatric practice medical schools are giving more and more attention to the well child and the pattern of his normal growth and development. As students are given an opportunity to observe and to examine well children and as they participate in the activities of well-baby clinics and child-health conferences with teachers and with parents, they become familiar with normal developmental processes and the child's potentialities for optimal health.

The study of normal growth and development is not limited to childhood; it is being expanded to include the whole natural history of man, extending through the years of maturation, the years of peak productivity and the years of declining energy. Arising from the fields of pediatrics and child psychiatry, greater attention is being given to the prematuration years in determining, in large measure, the individual's adaptation to the stresses of life and his ability to react to them in a manner conducive to physical and emotional health. Paul Lemkau, in his book *Mental Hygiene in Public Health*,[10] devotes more than half his pages to the genetic endowment of the individual and the periods of development up to the age of maturity. The teacher of pediatrics — he might better be called the teacher of child health — and the teacher of psychiatry have together found practical application of integrated teaching in bringing to the student an understanding of the cultural patterns, the influences of family relations and the social experiences that affect behavior and well-being.

Occupational Health

Secondly, occupational health, concerned as it is with all efforts to maintain the health of the worker at optimal level, provides another excellent demonstration of some of the practical values of a well conceived and well conducted health service. One of the methods used most successfully in bringing students to some understanding of health is to let them see for themselves the advantages that a progressive industrial plant derives from introducing a health program for its employees. The student is prompted to look for the answer to the following question: Why does industry, which generally measures success in terms of money, spend its money for the health of its workers? The answer is that it pays. This may be a somewhat surprising discovery for the student. The wizards of business and finance produce figures to show fewer compensation claims and less absenteeism and hospitalization, to say nothing of the gain in the well-being of the worker as he realizes that the boss really cares about his workers' health.

Considerable difference of opinion exists in medical schools concerning the amount of time that should be given to the teaching of industrial medicine. Much of the detail of this subject belongs more properly to graduate training of the physician who anticipates a career in industrial medicine. But, at the same time, direct observation of the services of medical departments of industrial plants provides a convincing demonstration of preventive medicine in action.

Military Medicine

The third field in which health is an object of direct study and research is that of military medi-

cine. Here, again, for very practical reasons, the optimum effectiveness of the human mechanism is of prime importance. The stresses that are encountered at high altitudes and in submarine and land warfare and the protection against these stresses are subjected to intensive research. Unfortunately, this field is so veiled by security restrictions that knowledge is not generally available. It is known, however, that these studies make use of physiologic and psychologic research in measuring man and his capacity for "the prodigal expenditure of energy" that Alan Gregg[8] has called one sign of health.

Independent Departmental Status

This discussion has now reached the point where attention may be given to one final question: Is an independent department of preventive medicine necessary or desirable in a medical school?

In British circles this question appears to have been answered definitely and affirmatively. The Social and Preventive Medicine Committee of the Royal College of Physicians of London,[11] in an interim report in 1943 made the following recommendations:

> (1) that every medical school should establish a department of social and preventive medicine, the size and scope of the department depending upon the facilities and personnel available; (2) that this department should organize a modernized course in social and preventive medicine to replace the present course in public health, which, as in the clinical subjects, should be a curriculum founded securely on the basic sciences, growing and expanding through the three clinical years; (3) that as well as theoretical teaching such a curriculum should bring the student into close touch with the active organizations in the community concerned, particularly with social and preventive medicine — namely, the health services provided by the local authorities, and the almoner's department within the hospital and (4) that all medical schools should recognize the importance of problems associated with industrial medicine.

In the United States, the question of departmental status for preventive medicine is still a matter of debate. Because preventive medicine has many affinities with other departments of the medical school and because many departments are now emphasizing the importance of the various levels at which prevention may be applied, some believe that separate departmental status is not necessary or desirable.

These arguments were given serious consideration at the Conference on Preventive Medicine referred to above, but in general they were not thought to outweigh the advantages to the medical school of one department primarily focused on the preventive aspects of medicine.

Admittedly, the kinds of knowledge and the kinds of skills in this field are indeed applicable far beyond the boundaries of segmented departmental teaching. It is, in fact, the general applicability of this knowledge and these skills that makes it desirable to assemble a corps of teachers expert in these matters in one place, so that their contribution may be assured of being available and may be used more advantageously throughout the school.

Although the teaching of preventive medicine is, or should be, the concern of many other departments and cannot be an exclusive concern of any single one, a department of preventive medicine, whose members are usually most familiar with overall community needs, organization and resources, is a particular asset in the development and conduct of extramural programs. Working out methods whereby students may gain meaningful experience with the application of medical care in the community has been and continues to be one of the particular contributions of departments of preventive medicine.

Conclusions

Finally, in summary and conclusion, I should like to re-emphasize three points.

In the first place, preventive medicine or social medicine is not a separate discipline with a discrete body of knowledge; rather, it is an attitude that permeates the entire medical curriculum. It is founded in the basic sciences and in clinical medicine; it also draws on the social sciences, and, in its application, calls for a health team that includes not only the practicing physician and the health officer but also the visiting nurse, the social worker and many others with specialized skills. As thus conceived, it is an essential part of medical education intended to develop a physician who, whatever his future field of activity, will be keenly conscious of opportunities to apply existing knowledge at various levels of prevention, to promote health, to construct barriers to disease, to interrupt its progression at the earliest possible moment or, preventive measures having failed, to limit disability as much as possible and to help the patient, even though he is permanently handicapped, to make the most out of life.

Secondly, the same fundamental educational principles are as important here as in any other part of the medical curriculum. The primary objective is to provide the student with an opportunity for increasing participation and responsibility in medical care under faculty supervision. Observation of environmental factors carries the student beyond the walls of the medical school and the university hospital. It becomes necessary for the student to gain first-hand experience from the home and from the community to appreciate the many and complex social forces that influence health and disease. Also, in the community, he becomes familiar with the various kinds of resources available both to benefit the public health and to aid the physician in serving individual patients. The department of preventive medicine is generally the part of the medical school most closely related to health programs and agencies of the com-

munity and hence, has rather special responsibilities in this respect.

Thirdly, in this still new era of medical care and medical education, there is need, not only for the exploration of new methods, but also for the application to these methods of the same sound scientific principles of research and evaluation that have brought diagnostic and therapeutic medicine to such high esteem. As they journey along this road, the physicians may number among their companions social scientists, cultural anthropologists and others with whom they have not been altogether familiar in the past. But the road leads forward with infinite possibilities toward a goal where the science of health will be established on a foundation as firm as that of the science of medicine today.

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MEDICAL PROGRESS

CANCER OF THE GENITOURINARY TRACT

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A REALISTIC appraisal of knowledge concerning neoplastic disease in general and that affecting the organs of the genitourinary tract in particular leads to the conclusion that, although the indefinite future may bring new chemical and enzymatic means of preventing, arresting or even curing neoplastic disease, the present generation at least must continue to rely on surgical and radiation technics as the only effective methods of control. Any improvement in terms of patient survival must depend on the better application of both methods.

This implies a continuation of effort to acquaint patients with the need for prompt recognition of danger symptoms and continued education of the medical profession to adopt a dynamic attitude toward the discovery of cancer, which means that any suspicious symptom or physical finding is considered probably due to cancer rather than the hope that it is not. This attitude implies insistence on prompt necessary examinations by competent physicians and specialists, which in turn necessitates the maintenance of increasingly efficient resident training programs. This will ensure surgeons and radiologists of superior attainments, capable of evaluating cases realistically and above all equipped to carry out procedures that have a real chance of eradicating neoplastic disease. Surgeons and radiologists must have as accurate knowledge as possible of the pathologic behavior and radiosensitivity of all lesions that they are called upon to treat. It seems unlikely that either surgery or radiation has reached the point of maximal effectiveness even in the hands of the best specialists.

Although it is obvious that development of new methods of treatment depends on basic research carried out in an effort to unravel the facts concerning etiology and development of cancer, because of the complexities of the chemical and physiologic problems involved, these studies must be conducted by relatively few trained or gifted persons. Most urologists must be content to devote themselves to improving the application of surgical and radiation technics now available, to be alert to the development of better methods and to school themselves on the basis of careful clinical observations to utilize initially the forms of therapy best suited to a particular lesion.

It appears to me that the last observation bears most careful scrutiny and that herein lies the cause of many failures. Many urologists are too optimistic about their ability to define the local microscopical extent of a cancer and therefore often recommend and carry out procedures that in fact have little chance of ridding the patient of disease. Radical surgery in urology is often attempted after conservative procedures have failed rather than as a primary form of therapy when it might be effective.

Cancer must theoretically and practically be con-

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sidered to fall, from the standpoint of evaluation and treatment, into three classes: first, lesions confined to the local organ capable of being totally removed if the cellular limits can be reasonably determined and proper surgical or radiologic methods applied; secondly, lesions grossly confined but with probable or actually demonstrable local surgically amenable extension or lymphatic spread; and thirdly, lesions too extensive locally for complete surgical removal, with or without metastases, or local disease capable of being removed with a margin associated with demonstrable distant lymphatic or vascular dissemination too extensive for conceivable curative therapy.

Obviously, many errors in evaluation and treatment arise because of inability to detect very early lymph-node or distant metastases arising from intravascular dissemination. Thus, many cases operated on appear to be in the first group that actually fall into the second or third. This is inevitable and accounts for many disappointments. In general, unless the metastatic lesions are susceptible to the effect of deep x-ray therapy, nothing but temporary improvement of local physiology is possible in such cases. The best examples to the contrary in urologic practice are to be found in the occasional case of solitary metastasis from renal-cell carcinoma or carcinoma of the bladder that may be surgically removed, and metastases from seminoma testis that are profoundly radiosensitive.

The main concern must be with the lesions in the first group, which offer an opportunity for real cure. In dealing with this group of cases one must see to it that surgical therapy is so carried out that local recurrence does not take place. Unfortunately, at present this goal cannot be attained with regularity. Perhaps one reason is that cancer may arise from more than one area in an organ—it may be of multicentric origin. The cases in the second group constitute a challenge to the urologist to find out whether local lymphatic and lymph-node spread from cancer of the penis, prostate, bladder, kidney, ureter or adrenal gland and testes may be surgically dealt with and at least some actual cures obtained. Except for cancer of the testes and penis this has only recently been attempted by urologic surgeons.

Judgment about treatment must be influenced not only by the demonstrable presence or absence of metastases but also to some extent by the degree of malignancy indicated by biopsy or study of the excised lesion, the duration of the lesion and its location. It is certainly true that many early lesions, by virtue of extreme degrees of malignancy, offer little chance of cure at any time owing to very early metastases. One must still do what one can. Conversely, some locally extensive lesions are without metastases and provide a good opportunity for radical surgical removal. Such lesions have demonstrated their low malignancy by long periods of growth without metastases. Experience alone allows the surgeon to recognize the possibility of surgery in such cases.

The present state of affairs in the treatment of neoplasms of the genitourinary tract is best presented by discussion of those encountered in each organ—adrenal gland, kidney, pelvis and ureter, bladder, prostate, testis and penis.

Adrenal Gland

Cortical Tumors

The surgery of adrenal tumors, because of special interests of general surgeons or urologists in different clinics, has been shared by both. However, the location of these glands above the kidneys, inability at times to differentiate adrenal and renal lesions, special diagnostic procedures largely utilized by urologists (retroperitoneal air injection and aortography), the introduction of bilateral adrenalectomy for advanced carcinoma of the prostate and the widespread use of the thoracoabdominal incision by urologists have all prompted urologists to undertake adrenal surgery.

A brief summary of lesions of the adrenal cortex that come up for differential diagnosis is difficult to write because of the varied clinical pictures resulting from bilateral hyperplasia, adenoma and carcinoma. Any of these three cortical lesions may be associated with the development of the adrenogenital syndrome or Cushing's disease,[1] depending on the type of adrenocortical cell or cells that undergo hyperplastic proliferation or neoplasia. The adrenogenital syndrome (female pseudohermaphroditism) is usually due to bilateral hyperplasia though carcinoma may be the cause. The condition is characterized by the development of exaggerated masculinity and is associated with increased urinary excretion of 17-ketosteroids.

An analysis of the pathological findings observed at autopsy in 98 cases of Cushing's disease by Plotz, Knowlton and Ragan[2] indicates an extraordinary variety of adrenal and pituitary lesions. There were 29 different possible combinations of lesions, all of which were associated with the same clinical picture. The combination most commonly met with was hyperplasia of the adrenal glands, with basophilic adenoma of the pituitary gland. The second most frequent was hyperplasia of the adrenal glands, with no pituitary abnormality except a characteristic hyaline change in the pituitary basophilic cells (Crooke[3]). Third most common was a malignant tumor of the adrenal glands, with hyaline changes in the pituitary basophilic cells. The benign adrenal adenoma occurred in only a small number of cases. Basophilic adenomas of the pituitary gland were found in a third of the patients. Adrenal lesions observed were bilateral hyperplasia in 58, carcinoma in 17 and adenoma in 11. Normal adrenal glands were present in 9 cases. It is interesting that basophilic adenomas of the pituitary gland were found in 24 cases in association with adrenal hyperplasia, and in 1 case with adenoma, but never with carcinoma. A good discussion of Cushing's disease is given by Knowlton.[1] Hormonal tumors

(adenomas or carcinomas) of the adrenal gland may be androgenic (masculinizing), estrogenic (feminizing), corticoid (Cushing's syndrome) or mixed (usually androgenic and corticoid). Nonhormonal tumors occur but are less frequent.

A presumptive diagnosis of hormone-producing tumors is usually suggested by the clinical picture supported by appropriate laboratory studies, including basal metabolic rate, glucose tolerance, electrolyte alteration and urinary steroid determination. All modalities of radiographic visualization—plain abdominal x-ray films, laminography, perirenal air insufflation either by injections through the flank or presacral areas, intravenous and retrograde pyelograms, aortography or combinations of these have been used to demonstrate space-occupying adrenal lesions. In the large carcinomas diagnosis is usually easy, but in bilateral hyperplasia, small adenomas or carcinomas the type of lesion or lateralization may be difficult to determine. Retroperitoneal air injection may be helpful, but fatal accidents from such injections have been reported and these studies cannot be carried out without slight danger.

Jailer[4] and Hodges[5] have independently called attention to a relatively simple means of distinguishing preoperatively between adrenal hyperplasia and adrenal carcinoma as the cause of the adrenogenital syndrome and Cushing's disease when the urinary 17-ketosteroid excretion is increased over the normal. This is based on the adrenal response or lack of response to diminution in the pituitary elaboration of ACTH induced by administration of cortisone. It is well known that patients with bilateral adrenal hyperplasia as the cause of the syndrome will respond to the administration of cortisone by a reduction in urinary 17-ketosteroid excretion. Hodges noted that in 1 case in which the adrenogenital syndrome was found at operation to be cortical carcinoma cortisone administration did not result in a lower urinary 17-ketosteroid excretion. He considered that the 17-ketosteroid response to cortisone administration constituted an important diagnostic test to differentiate benign and malignant lesions of the adrenal gland causing the adrenogenital syndrome. Jailer reasoned that the patient with Cushing's syndrome due to adrenal hyperplasia might respond similarly, whereas if there was an adrenal tumor whose cells were unresponsive to changes in pituitary stimulation, no change in the urinary excretion of 17-ketosteroids would be expected. He tested this hypothesis on 5 patients. The first 4, proved by operation to have bilateral adrenal hyperplasia, exhibited significant falls in urinary 17-ketosteroid excretion during four or five days of cortisone administration. In the fifth patient with adrenal carcinoma with metastases no decrease whatever occurred. It is well known that the adrenogenital patient with hyperplastic adrenal cortexes will respond to large doses of cortisone by a reduction in urinary 17-ketosteroid excretion (Wilkins). No patient with benign adenoma had been studied, but Harrison[6] reports that diminution of 17-ketosteroid excretion occurred in a patient with adenoma incident to cortisone administration, suggesting that cells of an adenoma may remain under pituitary control. If subsequent experience substantiates these observations this may provide a useful diagnostic aid in the differentiation of adrenocortical cancers from benign adenomas and bilateral hyperplasias in Cushing's disease and the adrenogenital syndrome.

Treatment. Patients with adrenogenital syndrome due to hyperplasia seem best treated by cortisone, which usually results in prompt decrease in 17-ketosteroid excretion and relief of symptoms. How long such treatment may be effectively continued is unknown. Publication of long-term results will be awaited with interest. The treatment of other adrenal lesions is surgical. An important fact, which must be carefully noted and which Jailer[7] emphasized, is that, when a tumor of the adrenal gland exists, the contralateral adrenal gland is invariably atrophic. Careful attention must therefore be given to proper administration of cortisone before and after operation.

At present the plan of surgical attack in this group of lesions is as follows: in Cushing's disease, if no definite tumor can be demonstrated by any of the refinements of radiologic diagnostic technics, bilateral simultaneous exposure of the adrenal glands is performed with the patient lying in the ventral position. Bilateral incisions are made through the bed of the twelfth ribs, or paravertebral incisions are made as described by Young. Both glands are dissected to allow complete inspection before any adrenal tissue is removed (this is to obviate removal of an atrophic adrenal gland in the presence of an adenoma in the opposite gland). If an adenoma is found, the gland containing it or simply the portion containing the adenoma is removed when possible. If bilateral hyperplasia is present complete removal of one and subtotal removal of the other probably constitutes the best therapy, though it may ultimately be found that complete bilateral adrenalectomy will give best results. Further clinical observations will settle this point. When bilateral adrenalectomy or subtotal removal is carried out constant observation to prevent alarming hypotension by intravenous administration of Neo-Synephrine or norepinephrine is necessary. Cortisone replacement by plan, as recommended by Huggins and Bergenstal,[8] Jailer[7] and others, is essential.

For removal of a well defined adrenal mass identified by diagnostic study a thoracoabdominal incision made through the bed of the resected tenth rib gives the best exposure, though a Nagamatsu[9] or an eleventh-rib extrapleural incision may suffice. A conventional lumbar incision is unsatisfactory. The thoracoabdominal incision, in my experience, provides the best exposure for adrenal surgery of this type, allowing dissection of the tumor under vision, careful hemostasis and opportunity for dissection of the gland from about

the great vessels if it seems desirable. Some of these tumors involve glands. Occasionally, the kidney may be involved, requiring nephrectomy as well. No large series of cases is available from which to estimate survival from adrenocortical carcinoma.

In my experience most patients have died from metastases. One definite reason for this has been long delay before diagnosis.

Medullary Tumors

Nonhormonal tumors of the adrenal medulla include the extremely malignant sympathicoblastomas sometimes classed as neuroblastomas and neurocytomas. Surgical removal seems to be the best treatment if metastases are not demonstrated.

The hormonal tumor of the adrenal medulla is the pheochromocytoma. According to Cahill[10] 8 per cent are malignant. About 16 per cent of patients have more than one tumor—usually two but rarely more. There is a familial tendency, and about 5 per cent have associated neurofibromatosis.

Symptoms may not be present. The tumor may be discovered accidentally by x-ray examination or at operative exploration, or in some cases death may occur during an operative procedure unrelated to the tumor. Cahill states that anesthesia has often precipitated a pressor attack in an unsuspected case. He warns that the occurrence of such an episode should cause abandonment of the operative procedure until the cause of the hypertensive episode has been ascertained.

Paroxysmal hypertension occurs in 30 to 40 per cent of the cases that are recognized. Persistent hypertension is frequently present by the time diagnosis is carried out. Seventy per cent of the patients described by Green[11] had more or less sustained hypertension. Cahill[12] states that patients with sustained hypertension who have a suggestive history of crisis or elevated basal metabolic rate, glycosuria or elevated blood sugar or who have severe sweating should be suspected of having pheochromocytoma. The presence of most or all of these symptoms suggests the desirability of specific tests and x-ray studies to rule out pheochromocytoma.

It has been demonstrated by Holton[13] and confirmed by Goldenberg et al.[14] that both epinephrine and nor-epinephrine are secreted by pheochromocytoma cells. The varied systemic response in patients with pheochromocytoma may well be due to relative amounts of epinephrine and nor-epinephrine secreted by the tumor. Nor-epinephrine causes little change in cardiac output and has little effect on the glycogenolytic rate and basal metabolism, but results in a significant increase in peripheral vascular resistance. Infusions of nor-epinephrine in normal subjects sufficient to produce a great rise in systolic and diastolic blood pressures result in no subjective symptoms. Infusions of epinephrine are almost always productive of headache, palpitation and a feeling of anxiety, with sweating. Epinephrine causes an increase in cardiac output and heart rate, with a fall in peripheral vascular resistance, and elevation of the glycogenolytic and basal metabolic rates.

In an effort to arrive at clinical diagnosis, tests have been devised both to provoke paroxysmal hypertension and to lower the blood pressure in such cases. Histamine, mecholyl bromide and tetraethyl ammonium bromide have been used for provocative tests. Cahill, who has used all these drugs, finds them without serious reaction, but he favors histamine because he thinks it is more reliable. In cases of severe hypertensive reaction Regitine must be available to prevent severe hypertensive crises.

Antagonists, through the depressor effect on epinephrine and nor-epinephrine, are benzodioxane (piperoxan), Dibenamine, and Regitine. Benzodioxane[15] has been found of value in distinguishing essential hypertension from the continuous hypertension seen in pheochromocytoma. When it is given intravenously to a patient with tumor both systolic and diastolic pressures fall significantly and rapidly and soon return to or above previous levels. No change or pressure effect is noted in patients with hypertension from other causes than pheochromocytoma. Dibenamine (Hecht and Anderson[16]) has a depressor effect, which may last for twenty-four to forty-eight hours. The drug is used for therapeutic control of paroxysms prior to or during operative procedures, rather than for diagnosis, since it has a depressor effect in both normal persons and patients with tumors. Regitine (Grimson et al.[17]) is useful as a diagnostic test and as a therapeutic aid at the time of operation. It produces a more pronounced and prolonged reduction in blood pressure than Benzodioxane when used as a diagnostic test, and its therapeutic effect is greater. It has proved less toxic and more easily controlled.

Cahill[10] calls attention to recent as yet unpublished work by Goldenberg regarding determination of epinephrine and nor-epinephrine (catechols) excretion in the urine. He has found that patients with pheochromocytoma during crises or when pressure is sustained, excrete large amounts, and suggests that this test may prove to be diagnostically very useful.

Radiographic localization and visualization of these tumors involves the same technic used for the delineation of adrenocortical lesions. Retroperitoneal air injection has been very helpful in Cahill's experience for the localization of small tumors. He calls attention to the fact that pheochromocytomas are often visualized as ovoid or circular shadows less dense than the surrounding tissues. Some extraadrenal tumors may be outlined by retroperitoneal air if properly located.

Treatment is surgical removal. Surgery may be made safe by the use of Dibenamine or Regitine, preferably Regitine before and during operation to prevent paroxysms of hypertension associated with anesthesia or manipulation of the tumor. After the tumor has been removed under Regitine therapy a

hypotensive crisis may be prevented or controlled by intravenous effusion of nor-epinephrine since Regitine only partially suppresses nor-epinephrine effect. The drug is usually given intravenously an hour or two before operation in a 5-mg. dose. During operation it is continued in doses of 0.08 to 0.33 gm. per kilogram of body weight. Anesthesia must be induced by agents that do not contribute to ventricular arrhythmias in the presence of epinephrine. Ether and oxygen are preferred by Cahill. Of 14 patients operated on for pheochromocytoma at the Presbyterian Hospital in New York City, 4 died as a result of operation. Seven patients have been operated on since 1946, without a death.

Tumors located in the region of the adrenal gland may be excised if accurately localized through the thoracoabdominal or Nagamatsu incision, but since 16 per cent are multiple and variably located, a transverse transperitoneal approach seems to be the most satisfactory and is recommended by Cahill.

Renal Tumors

For purposes of this discussion renal tumors may be divided into three groups: Wilms tumor, renal-cell carcinomas and carcinomas of the renal pelvis and ureter (ureteral tumors are included because therapy for pelvic and ureteral tumors is essentially the same). Benign adenomas, benign connective-tissue tumors and sarcomas occur but are relatively rare.

Wilms Tumors

Wilms tumors require no special comment from the diagnostic standpoint since they occur, by and large, in infants or children and are usually recognized by virtue of the appearance of a palpable mass. This means that in terms of chronologic development they generally come up for treatment late in view of the fact that they occur in the renal area under the rib cage; there seems to be no practical method of avoiding this delay. Diagnosis is usually suggested by the location of the mass and confirmed by intravenous or retrograde pyelograms. On the basis of the work at the Children's Hospital in Boston there seems to be little doubt that prompt surgery, followed by deep x-ray therapy to the operated area, offers the best prognosis. It is good in infants under one year and less so afterwards. Gross and Neuhauser[18] report that of 38 patients operated on between 1940 and 1947 47.3 per cent survived and, most important, of 18 under one year of age 80 per cent survived. Transperitoneal nephrectomy was done with postoperative irradiation to the renal fossa of 200 r daily, three ports being used alternately for a total of 4000 to 5000 r in air. No cures followed irradiation of pulmonary metastases though life appears to have been prolonged. These statistics are in general far better than others reported.

Renal-Cell Carcinoma

Renal-cell cancers are still subject to considerable pathological disagreement. One—and perhaps the most satisfactory—way of thinking of these tumors is to divide them into two groups: clear-cell and dark-cell types. It is true that this division is not entirely satisfactory because there may be overlapping, but it is useful from the standpoint of prognosis. The clear-cell tumor, which has previously been termed hypernephroma or Grawitz tumor, is characterized by large, clear cells with small nuclei. The tumor is grossly well defined though not truly encapsulated. It does not actively invade the renal substance about it and does not involve local lymph nodes but does metastasize by the blood stream. Metastases are occasionally single and sometimes so located, in lung or bone, that surgical removal of the primary and secondary lesion is possible. One might describe this lesion as a locally benign but metastasizing cancer. Prognosis is reasonably good. On the other hand the dark-cell tumor is a much more malignant lesion. There is no uniform cellular pattern, but the cells by-and-large are smaller with more nuclear material. It actively invades the renal substance and renal capsule and frequently extends into the perirenal fat and fascia, producing fixation. There is often lymphatic extension to local lymph nodes and blood-borne metastases occur widely. The prognosis is grave.

Unfortunately, the diagnosis is usually made quite late because of insignificant early symptoms. Hematuria, mass and pain in the renal area are the classic symptoms but are absent in many cases or occur late in the development of a tumor. In a significant number of patients these symptoms are lacking, and the lesion is ultimately diagnosed by virtue of cachexia, unexplained anemia or fever. It seems that early diagnosis is impossible in most cases. Metastatic lesions may initiate a search that leads to the diagnosis of a renal lesion.

However, at the New England Medical Center[19] it has been observed that, when plain x-ray films of the abdomen are satisfactory, renal outlines are usually well visualized, and it has become standard practice to recommend intravenous urography when the renal shadows suggest a space-filling abnormality. In this way renal cysts and occasional renal tumors have been discovered in patients without symptoms suggesting such lesions. If a plan like this could be adopted in all hospitals it might contribute to much earlier diagnosis of renal neoplasms. Needless to say, a plain film of the abdomen should be included in any diagnostic study or group survey not only because of the renal aspect but also because of much additional information to be obtained.

Once attention has been called to a mass in or about the kidney the problem of determining its nature if possible remains. Palpation may be helpful by demonstrating a firm or irregular mass. Calcification cen-

trally located usually means neoplasm. Study of the urinary sediment by Papanicolaou stain has occasionally been of value. Many diagnostic procedures have been recommended, and any or all may be helpful at times. In the average case, the procedure should be to utilize only the tests that are necessary to arrive at diagnosis on which treatment may be based rather than the accumulation of excellent x-ray films illustrating the respective value of any method. An important limiting factor these days is expense.

A sound method of procedure is first to obtain an intravenous urogram, which usually, unless the kidney is nonfunctioning, allows one to make a shrewd guess about the diagnosis. For instance, one can usually decide whether the mass represents a renal or an adrenal lesion. A retrograde pyelogram may be obtained if the pelvis and calyceal visualization is not good and better visualization might be of value. Calcification in the central portion of the renal lesion is very suggestive of a renal tumor. In the series of 82 renal tumors studied by Cahill and Melicow,[12] calcification was found in 15 per cent. At this point a helpful simple diagnostic study is to obtain laminograms or tomograms, which in many cases allow the differential diagnosis of renal, adrenal or other retroperitoneal mass and sometimes, by virtue of the mass contour, permits a positive diagnosis of polycystic or multicystic kidney. The chief diagnostic difficulty lies in the differentiation of a simple cyst, cystic tumor (papillary cystadenoma) or cortical neoplasm of the kidney. To distinguish between cyst and cystic tumor may be impossible short of pathological study of the excised lesion, but differentiation of cyst or cystic tumor and renal-cell carcinoma is now quite possible in most cases by either nephrotomography or aortography.

Nephrography, described by Vesey, Dotter and Steinberg,[20] of the New York Hospital, is much simpler and when successful provides a striking radiogram. When a cyst is present nephrography demonstrates a renal shadow of considerable density owing to dye in the capillaries and tubules of the kidney, with a round, punched-out area of radiolucence corresponding to the mass visualized on the plain x-ray film and pyelogram. This results from absence of parenchyma in this area. When tumor is present the area of tumor may be essentially of the same density as that of the functioning kidney, but irregular pooling of the contrast substance may be noted. Evans, Dubilier and Monteith,[21] of the New York Hospital, improved this procedure by first determining by tomography the plane in the body that shows the tumor outline best, and then taking films after the injection of concentrated Urokon to produce a nephrogram. This technic has been called nephrotomography. The method described by Evans et al.[21] is as follows: the patient is placed in the supine position on a roentgenographic table equipped for tomograms; preliminary plain films and tomograms are obtained to be used as control films and to check the roentgenographic technic; a 12-gauge Robb–Steinberg angiocardiographic needle is inserted into an antecubital vein; arm-to-tongue (Decholin) circulation time is determined, employing the same injection technic as for the contrast substance; before the Urokon is injected it is advisable to rehearse the injections with the patient and to warn of the sensations to be expected so that there will be no movement or breathing during the exposures; and, finally, with the x-ray tube in midposition, 50 cc. of 70 per cent Urokon sodium is rapidly injected (in one and a half to two seconds) into the antecubital vein. A film is then exposed at the predetermined circulation time. The first roentgenogram will demonstrate the renal arteries. This is followed as rapidly as possible by a second film, which secures the nephrogram. Immediately after the second exposure a tomogram is obtained. The elapsed time between the first exposure and the completion of the tomogram should not exceed twenty-five seconds.

This technic, in my experience, is one of the most helpful in differentiating cysts and tumors of the kidney.

The same information, as well as better visualization of the renal arteries, may be obtained by aortography performed either by aortic puncture through the left lumbar area or by surgical exposure of the femoral artery and catheterization of the aorta through a needle into which a polyethylene catheter is threaded to the desired level. Various modifications of these technics have been utilized. Aortography has been combined with perirenal air insufflation via the presacral route in an effort to obtain additional information. Any or all of these procedures may provide information that is helpful, but owing to technical difficulties or the very nature of the disease a correct preoperative diagnosis cannot always be made. Ainsworth and Vest[22] point out that when a large cyst is suspected simple aspiration through an 18-gauge needle introduced through the lumbar area followed by injection of Diodrast and x-ray study will confirm the diagnosis. They also state that the chance of inserting the needle into a malignant tumor is remote. When the suspected cyst is small or centrally located in the hilar region aspiration should not be done, in their opinion. On theoretical grounds the possibility of entering a papillary cystadenoma and spilling cells into the needle tract, which would almost certainly result in local implantation of cells, makes this procedure inadvisable. However, the frequency of papillary cystadenoma is small so that practically this risk is not great. In a few cases in which the diagnosis of cyst seemed quite certain this technic has provided excellent visualization of cysts.

The object of this careful diagnostic study is to be able to plan treatment. Whatever the symptoms, when diagnostic studies point clearly to the diagnosis of renal cancer (without demonstrable metastases or in the presence of operable metastases), one should lose

no time in carrying out nephrectomy. The objective should be, first of all, to dissect, under direct vision, the intact Gerota fascia containing the kidney from the diaphragm, lumbar muscles and adjacent peritoneum (unless there is evidence of involvement or near involvement of overlying peritoneum, in which case the peritoneum overlying the renal mass should be removed with the kidney). The second object is to explore the abdomen and lung for metastases. Thirdly, ligation of collateral venous channels from within Gerota's fascia at their points of emergence on the diaphragm or lumbar muscles or beneath the peritoneum is performed to minimize blood loss and allow gentle mobilization of the mass to the pedicle area; when the main renal vein is partially blocked by the tumor these vessels constitute, in effect, the pedicle of the vein. If the lesion is large and in the upper pole the adrenal gland should be included in the dissection since one cannot be certain whether microscopic perforation of the renal capsule, with involvement of fat within Gerota's fascia, has occurred and preservation of the gland interferes with complete removal of these structures. Fourthly, the renal artery on the aorta, which is normally located superior to and slightly posterior to the vein, is exposed; this should always be isolated, clamped, divided and ligated before the vein is interrupted to prevent engorgement of the kidney and trapping of blood, which would thus be removed from the circulation. Once the artery has been severed the vein collapses and can be clamped and divided with safety and ease. If tumor is palpated in the vein it should be gently freed to its junction with the vena cava and clamped and divided below the tumor. If tumor extends into the vena cava the vessel should be occluded temporarily between clamps and opened to allow removal of tumor under vision and then carefully closed; if the vena cava is involved by tumor it should be resected in such a way that the orifice of the opposite renal vein is not occluded. Right-sided tumors can be dealt with easily in this way. Left-sided tumors, with involvement of the vena cava, present a problem. Finally, connective tissue and glands are dissected from the aorta or the vena cava, depending on the side, if indication of gland involvement is found.

Operation conducted in this manner is as radical as any that can be devised. It can be actually accomplished safely only by the use of the thoracoabdominal or Nagamatsu incision or a generous abdominal incision for large tumors and tumors of the upper pole. If the thoracoabdominal incision is to be employed the tenth rib should be dissected back to its angle, and the diaphragm incised sufficiently to allow generous exposure of the suprarenal area. In my opinion, based on considerable experience, the lumbar incision should never be considered adequate for the removal of a renal tumor, and the transabdominal approach is much less satisfactory than the transthoracic. Although no publication of any significance has followed that of Chute, Soutter and Kerr,[23] in 1949, and Chute,[24] in 1951, and insufficient time has elapsed for one to compare the results of nephrectomy through this incision with those of less satisfactory technics, the procedure has been widely used so that statistical appraisal will soon be possible.

How should exploration of the kidney be carried out when the diagnosis of tumor is suspected? My plan is to make the thoracic portion of the thoracoabdominal incision and palpate the kidney through the intact Gerota fascia. If the lesion is firm and unmistakably tumor the abdominal portion of the incision is completed, and radical nephrectomy done. If palpation suggests cyst the surface of the lesion is explored by incision of Gerota's fascia as necessary. If the surface of the cyst suggests simple cyst it is aspirated, opened and inspected for signs of tumor. If the cyst suggests papillary cystadenoma because of the presence of bloody fluid, Gerota's fascia is closed, and radical nephrectomy done. When one is dealing with a small intrarenal lesion the kidney must be carefully inspected, and the questionable area needled, after the wound has been carefully packed off. If no fluid can be aspirated two courses are possible; open incision of the kidney[25] after exposure and temporary occlusion of the pedicle; and nephrectomy. The first seems desirable even though when tumor is present there is a chance of cell spillage. Renal aortography at the time of operation may be of diagnostic aid in an occasional case.

The results of nephrectomy for renal cancer in the past have been discouraging. For instance, a recent analysis by Deming[26] of 132 cases indicates only a 9 per cent control. Metastases may become obvious more than ten years after nephrectomy so that a ten-year follow-up period is necessary for worthwhile evaluation. Foote, Humphreys and Whitmore[27] analyzed 85 patients with determinate renal-cell carcinoma; 38 per cent were alive five years later, and of 40 followed for ten years 22 per cent were alive. Dick and Flint[28] found a 46 per cent five-year survival in a study of 26 cases. These figures indicate that there is much room for improvement in the management of this type of cancer.

Tumors of Renal Pelvis and Ureter

These tumors are classified in the same fashion as bladder lesions—papilloma, papillary transitional-cell carcinoma and primary infiltrating epidermoid or frankly squamous carcinoma. The last is frequently associated with long-standing infection and calculi. Hematuria and pain that is due to developing hydronephrosis from obstruction are the common symptoms. The diagnosis can usually be made by intravenous or retrograde pyelograms demonstrating filling defects or obstructions in the pelvis or ureter, which are usually quite characteristic. Study of the urinary sediment by Papanicolaou technic often gives confirmatory evidence.

Treatment

If a papilloma is solitary it can, when necessary (as in a solitary kidney) as reported by Vest[29] and Leadbetter,[30] be treated with reasonable confidence by ureterotomy or pyelotomy, with excision or fulguration. Usually—and always in the presence of multiple papillomas or papillary carcinomas—complete nephroureterectomy and removal of a cuff of bladder are required because of the possibility of implantation of cells or of incipient lesions of multicentric origin. Such papillary carcinomas may metastasize by the blood stream, but involve local lymphatics and retroperitoneal lymph nodes late or infrequently so that one need not worry much about local metastases in these cases. On the other hand epidermoid lesions of the pelvis or ureter are characterized by early lymphatic involvement and have generally proved fatal. It seems in such cases that a very radical nephroureterectomy removing all perirenal and periureteral fat and fascia, combined with a very careful retroperitoneal-lymph-node dissection, might offer some hope if lymphatic spread is minimal. I have performed such an operation on one occasion in which numerous lymph nodes were removed, but in this case residual lymphatic disease was present and the patient died. This procedure should be done more generally.

Foote, Humphreys and Whitmore[27] found 1 five-year survival in a study of 19 patients with transitional-cell carcinoma of the renal pelvis. This patient died of cancer in the seventh year. Seven patients with papilloma survived for five years. Dick and Flint[28] reported a 25 per cent five-year survival in 12 patients with transitional-cell tumor of the renal pelvis. Oberkircher, Staubitz and Blick[31] presented 15 cases of squamous-cell carcinoma of the renal pelvis without a five-year survival. The average postoperative survival was twelve and seven-tenths months. Higgins,[32] in a study of 47 tumors of the renal pelvis, found 7 squamous-cell carcinomas. All patients died. Of 31 patients with papillary carcinoma in his series 16 were alive and well; 11 died from metastases, and 5 from unrelated causes.

These discouraging findings indicate the great need for earlier diagnosis and much more adequate surgical therapy.

Bladder Cancer

No field in urology is characterized by so much discussion concerning proper therapy. This stems largely from poor results obtained to date in the treatment of infiltrating cancers. As indicated above, in the discussion of tumors in the renal pelvis and ureter, tumors of the bladder may be divided into papillomas, papillary transitional-cell carcinomas and primary infiltrating carcinomas. Diagnosis is made by cystoscopic examination prompted by hematuria or urinary symptoms of frequency, pain on urination or flank pain resulting from developing obstruction of a ureter. Cystoscopic examination usually allows decision about the number, type and location of tumors and the presence or absence of significant infiltration of the bladder wall. Biopsy should be done in such a way that multiple, deeper portions of the tumor, if possible, in relation to the bladder wall itself, are removed. It will provide a specific microscopical pattern or patterns. Bimanual rectoabdominal or vaginal abdominal examination, as first suggested by Jewett,[33] gives valuable information regarding the size and depth of infiltration or fixation of tumors. This, together with intravenous urography and x-ray study of the chest and bony skeleton, provides information on which therapy may be planned.

The pathological characteristics of bladder tumors may be summed up by the statement that superficial papillary cancers do not generally involve lymphatics, perhaps because there are no lymphatics in the mucosa of the bladder, but it should be noted that these tumors, even as they begin to infiltrate the bladder muscle, seem to invade lymphatics more slowly than epidermoid lesions. They do occasionally metastasize by the blood stream. Behavior in this respect is probably a function of the degree of malignancy. Areas of epidermoid or squamous-cell conversion in transitional-cell cancers are often found and, if present, require that the lesions be classified as epidermoid or squamous-cell cancers. Melicow[34] and Masina[35] have called attention to the common occurrence of multiple areas of metaplastic change affecting the bladder mucosa in patients with tumors of the bladder. This may account for recurrence of tumor after apparently successful therapy of a lesion—the multicentric origin of tumors. Masina suggests multiple biopsies of the bladder mucosa away from obvious tumor as a guide to therapy. Primary infiltrating epidermoid or squamous-cell cancer, in most cases, behaves differently from papillary transitional-cell cancer in that it infiltrates the bladder muscle early and is disseminated both by the local lymphatics to the pelvic lymph nodes and by blood-vessel invasion to bones or viscera. Jewett and his associates[36-40] have repeatedly called attention to the relation between depths of penetration of cancer into the bladder wall and lymphatic dissemination. They have shown that, if the deeper layers of the bladder wall or perivesical tissues are involved, cure by any method of treatment is difficult. My own experience indicates that when involvement of pelvic lymph nodes has occurred, cure by present surgical methods is unlikely. These observations form the basis of planned therapy.

(To be concluded)

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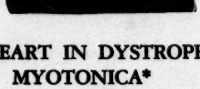
MEDICAL INTELLIGENCE



THE HEART IN DYSTROPHIA MYOTONICA*

Report of an Autopsied Case

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IN a recent review[1] of 85 cases of dystrophia myotonica in which electrocardiographic, roentgenographic or anatomic data, or all, were available it was found that most of the patients manifested changes suggestive or diagnostic of heart disease. Only a few cases were studied post mortem, and in most the description of the heart left much to be desired.[2-7] Recently, we had the opportunity to study a patient with dystrophia myotonica who manifested atrial flutter and died of acute heart failure. The anatomic changes in the heart were striking and form the basis of this report.

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CASE REPORT

W.D., a 41-year-old man, was seen at the Indianapolis General Hospital on December 2, 1952, complaining of muscular weakness and weight loss of 14.5 kg. About 10 years previously he had noticed inability to relax his grip. Four years later he observed progressive weakness and wasting of the upper and lower extremities and development of a cataract in the right eye. He denied symptoms referable to the cardiovascular system. No loss of libido or impotence was noticed. The past medical history was otherwise noncontributory.

The family history disclosed that the patient's father had died at the age of 82 of unknown cause. The mother was alive and well at the age of 75. Six siblings were living and well. The patient had 3 children, 1 of whom, a 17-year-old boy, had dystrophia myotonica.

Physical examination disclosed an emaciated man who was 175 cm. tall and weighed 61 kg. He was oriented regarding time, place and person. The eyes were sunken. Frontal baldness was striking. Examination of the eyes disclosed a cataract in the right eye that prevented visualization of the fundus. The respiratory system was normal. Blood pressure was 105/65. The heart rate varied from 60 to 90 beats per minute, suggesting atrial flutter. The heart was not enlarged. No thrills or shocks were palpable. The apical sounds were somewhat distant, but no murmurs were heard. Examination of the abdomen, rectum and prostate disclosed no abnormalities. The right testicle was smaller than normal.

The facies were typically myopathic, with lack of emotional expression. The sternocleidomastoid muscles were reduced to strands. There was generalized muscular weakness and atrophy, especially of the upper and lower extremities. The sensorium was intact. Deep reflexes were diminished.

Laboratory studies disclosed a negative serologic test for syphilis and normal hemogram and urinalysis. Determinations of basal metabolism on 2 occasions were unsatisfactory because of poor co-operation. The fasting blood sugar and serum cholesterol were within normal limits; 17-ketosteroids were 10.6 mg. per 24 hours.

A roentgenogram of the chest showed no abnormalities of the lungs or heart. An electrocardiogram (Fig. 1) taken on January 18, 1953, demonstrated atrial flutter, with a varying degree of block. The heart was rotated clockwise. No other significant abnormalities were noted.

The patient was released from the hospital on January 20. Little was known of the intervening period before death, which occurred on January 27. On the evening of death, while walking with his son, he suddenly became unconscious, dying shortly thereafter.

Autopsy was performed about 12 hours after death. Only pertinent findings will be reported.

In the anterior mediastinum there was a fairly large thymus, 50 gm. in weight and measuring 13 by 5.5 by 10 cm. The heart was soft and flabby and weighed 340 gm. The

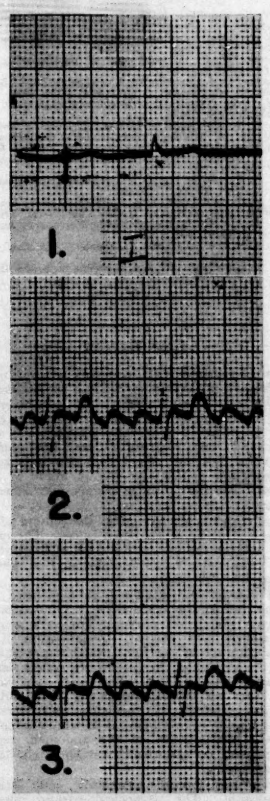

FIGURE 1. *Electrocardiogram Taken on January 18, 1953, Showing Atrial Flutter, with a Varying Degree of Block and Clockwise Rotation.*

coronary vessels were normal. The walls of the left and right ventricles were about 1.2 cm. and 0.4 cm. in thickness. The diameter of the aortic, mitral, pulmonic and tricuspid valves was 7, 10.5, 7.5 and 12.5 cm. respectively; the valve leaflets were normal. There were several areas within the wall of the left ventricle that were dark red, linear in shape and measuring about 2 mm. in length. These appeared to be hemorrhagic. Mottled, tiny, gray areas were scattered through the myocardium.

The left lung weighed 900, and the right 1000 gm. Both lungs appeared moderately enlarged and firm to palpation. The lower lobes were dark red. A moderate amount of gray, mucoid material was present in the bronchi. Cut section showed the surface to be dark red, glistening and of rubbery consistence.

The liver weighed 2020 gm. and on cut sections appeared moderately congested.

The spleen weighed 340 gm. The capsule was slate blue.

FIGURE 2. *Section through the Left Ventricle, Showing Atrophy of the Myocardial Muscle, with Fibrous Replacement.*

Cut sections revealed moderate congestion, with a purplish-red color.

The right testicle was soft and smaller than normal. The left testicle appeared normal.

Microscopical section from the left atrium showed a moderate amount of fatty infiltration. Sections through the

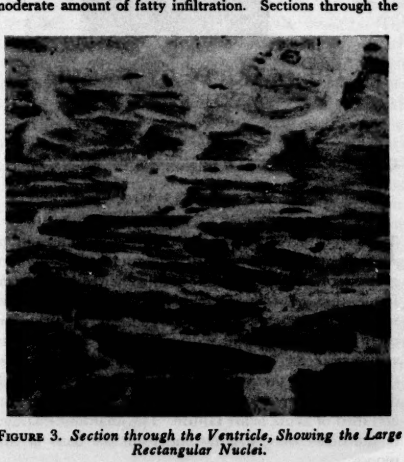

FIGURE 3. *Section through the Ventricle, Showing the Large Rectangular Nuclei.*

papillary muscles of the left ventricle and its wall disclosed diffuse fibrosis, with separation of muscle fibers by fairly dense, fibrous connective tissue (Fig. 2). Hypertrophied muscle fibers, with large rectangular nuclei, were scattered throughout (Fig. 3).

The lungs demonstrated severe congestion and edema.

Sections of the liver showed numerous tiny foci of liver-cell necrosis, with accompanying foci of polymorphonuclear

infiltration. Moderate lymphocytic infiltration was present about the triad areas. Connective tissue was normal in amount. Most of the liver cells revealed cloudy swelling.

The thymus contained normal-appearing lobules, with prominent Hassall corpuscles, many of which were partially calcified.

One section of skeletal muscle disclosed scattered, small foci of lymphocytic infiltration. Other sections revealed no abnormalities.

Discussion

Atrophy of the myocardium and variability in size of fibers with variation in nuclear size and shape were described by Fagin[6] and Black and Ravin.[7] The type of fibrous replacement of myocardium in the presence of normal coronary vessels, as observed in the case presented above, has not hitherto been reported. There is little doubt that the cardiac disease caused the patient's death. It would not be profitable to conjecture about the exact mechanism of the myocardial change as long as the basic cause of the disease remains obscure. However, it may be assumed that, in the absence of the usual causes of heart disease, the pathologic alterations may be a part of the underlying process. Future study of similar cases may help to shed some light on this very interesting form of heart disease.

Summary

A case of dystrophia myotonica, with clinical and anatomic evidence of heart disease, is reported.

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 40381

Presentation of Case

A sixty-four-year-old retired bartender was referred to the hospital because of anemia, weight loss and constipation.

He had been in good health until five months previously, when pain and stiffness in the shoulders, elbows, fingers and knees developed. His physician diagnosed the condition as "arthritis" and prescribed small white tablets, which the patient took three or four times a day, with relief of symptoms. At the same time the physician prescribed an oral iron-containing medication although the patient was not told whether or not he was anemic. At about the same time he began to be constipated and was given various kinds of pills, which helped somewhat. In the previous four months he had lost 25 pounds in weight despite good appetite and adequate food intake. The stools had been repeatedly black—a fact that he attributed to the iron pills. He denied gross blood in the stool. Constipation became gradually worse so that for the preceding week he had had no bowel movements despite many laxatives.

The patient denied nausea, vomiting, jaundice or blood loss of any sort. He had drunk moderately heavily for many years while a bartender but allegedly stopped drinking three months before admission because of lack of funds and because of vague abdominal "gas pains," which then disappeared. He had been rejected for military service during World War I because of a "leaking heart valve" although he denied a history of rheumatic fever. Five years before entry he had been hospitalized for a rectal abscess.

Physical examination revealed a thin, malnourished, pale, chronically ill man in no distress. Several small, nontender, shotty lymph nodes were palpated in the posterior cervical and axillary regions bilaterally. The chest was emphysematous, and some rales were heard at both bases. The heart was not enlarged on physical examination; the sounds were distant, no murmurs were heard, and the cardiac rhythm was normal. There was some voluntary muscle spasm that made abdominal examination difficult. The liver edge was felt 3 fingerbreadths below the right costal margin; the spleen was 3 fingerbreadths below the left costal margin. There was no fluid wave and no shifting dullness. Rectal examination disclosed large, painful, internal hemorrhoids; the prostate was diffusely enlarged to twice the normal size, and was soft to palpation. There was no peripheral edema. Neurologic examination was negative.

The temperature was 99°F., the pulse 88, and the respirations 24. The blood pressure was 118 systolic, 62 diastolic.

Urinalysis was negative. Examination of the blood showed a hemoglobin of 7.5 gm. per 100 cc. and a white-cell count of 1500, with 12 per cent neutrophils, 74 per cent lymphocytes, 2 per cent prolymphocytes and 12 per cent monocytes. The red cells were normochromic and slightly microcytic; the reticulocytes were 0.8 per cent, and the platelets were normal on the smear. The prothrombin time was 70 per cent of normal. The nonprotein nitrogen was 21 mg., the albumin 2.5 gm., the globulin 3.6 gm., the total bilirubin 0.3 mg., the alkaline phosphatase 1.9 units, and the serum iron 50 microgm. (normal, 125 to 200 microgm.) per 100 cc. A bromsulfalein test showed 4 per cent retention of the dye at the end of forty-five minutes, and the cephalin flocculation was + + + after twenty-four and + + + + after forty-eight hours. The Coombs antiglobulin test was negative, as was a serologic test for syphilis. The stools were repeatedly negative for occult blood.

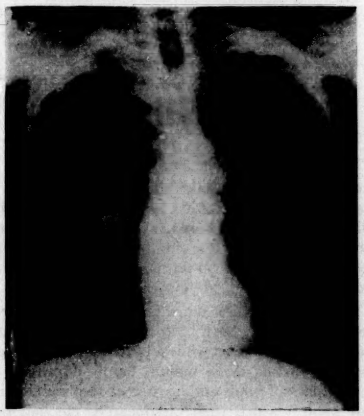

FIGURE 1.

A roentgenogram of the chest disclosed scattered, ill defined areas of increased density throughout both lung fields (Fig. 1). The right hilus was somewhat full in appearance, suggesting the presence of lymph nodes. There was pleural thickening of both apexes. The right costophrenic angle was blunted. The heart was not enlarged. Roentgenographic studies of the abdomen showed the splenic shadow to be enlarged and the tip of the liver to lie at the level of the iliac crest. There was a normal bowel pattern. Barium studies of the esophagus, stomach and duodenum were not remarkable. In a barium-enema examination the barium readily filled the colon, without evidence of a gross obstructing lesion or filling defect. Although evacuation was complete, the mucosa did not coat well, and the radiologists stated that small polypoid lesions could not be excluded. Intravenous pyelography demonstrated prompt excretion of the dye bilaterally. The calyceal pattern was normal; there was some displacement of the left upper urinary tract, particularly the calyxes and pelvis toward the midline, presumably because of an enlarged spleen. A survey series gave no evidence of metastases in the skull, thoracic and lumbar spine, hips or pelvis.

Aspiration of the sternal bone marrow yielded smears that showed 20 per cent erythroid elements, 33 per cent mature lymphocytes, 8 per cent monocytes, 1 per cent plasma cells and 39 per cent granulocytes. The granulocytes were almost all myelocytes, and only an occasional mature polymorphonuclear leukocyte was present. No blast forms and no tumor cells were identified; megakaryocytes were normal.

Skin tests for tuberculosis sensitivity (purified-protein derivative) were negative after forty-eight hours in the second strength; the histoplasma skin test was negative. Biopsy of an axillary lymph node was interpreted as showing chronic lymphadenitis with fibrosis. Peritoneoscopic examination disclosed that the peritoneal surfaces were normal; the liver was enlarged and had a smooth, normal-colored external surface. The spleen was also enlarged, and there were two deep clefts along the anteromedial margin. On the inferior tip there was a 2-cm. white plaque with several surrounding smaller plaques. The diagnostic significance of these was not known. Liver biopsy obtained from the left lobe during peritoneoscopic study disclosed slight extramedullary hematopoiesis. There was no evidence of retroperitoneal disease at the time of peritoneoscopy.

Seven days after admission the patient had a sudden attack of atrial fibrillation that was successfully treated with digitalis. Several electrocardiograms taken after digitalization disclosed right-bundle-branch block. Digitalis and Mercuhydrin were continued, and the cardiac status remained unchanged. He was treated with multiple, small blood transfusions, penicillin and intravenous infusions of glucose. Proctoscopic examination confirmed the findings of mild perianal inflammation, with a small fistula in ano. No tumor was observed. He became progressively weaker, and persistent cough developed, with a small amount of yellow sputum. The temperature rose to 102°F. and remained elevated for three days before returning to normal. He had several short febrile episodes, separated by ten to fourteen days of normal temperature. Repeated roentgenographic examinations of the chest disclosed a large area of consolidation in the right upper lobe, with some fluid (Fig. 2). Sputum cultures demonstrated abundant alpha-hemolytic streptococci and a moderate growth of *Neisseria catarrhalis*. Smears for acid-fast bacilli were repeatedly negative. *Candida albicans* was present on one smear. Six smears of the sputum were examined for malignant cells; two were negative, two doubtful, and two unsatisfactory. One blood-culture flask grew *Staphylococcus aureus;* three were negative for bacterial growth.

Bronchoscopic examination showed diffuse reddening throughout the tracheobronchial tree; the orifices of all the lobes appeared free of disease. The white-cell count varied from 1750 to 400 and was usually below 1000. The differential count remained unchanged. The blood hemoglobin level remained about 11 gm. per 100 cc. with numerous transfusions. The patient's condition gradually deteriorated. Numerous antibacterial medications produced no change, nor was there any clinical or hematologic improvement after 600 r of radiation to the spleen. Cortisone was administered for two weeks, and although he felt better, there was no objective evidence of benefit.

On the seventy-third hospital day an operation was performed.

Differential Diagnosis

Dr. John Norcross*: This is a complicated story. Investigation revealed widespread disease involving particularly the lungs, the lymph nodes, the liver, the spleen and the bone marrow. With this condition there was an intermittent fever. Before going into more detail I should like to see the x-ray films.

Dr. Joseph Hanelin: During the period of nearly four months in the hospital many films were taken. I shall show only a few of them. The abdominal films demonstrate enlargement of the liver and spleen. The stomach and colon are normal; there are some prominent gastric folds and a small hiatus hernia. An intravenous pyelogram reveals good function of both kidneys, with normal calyceal patterns. The left kidney, however, is displaced somewhat medially, probably as the result of pressure from the spleen. No esophageal varices are apparent in the gastrointestinal films.

Dr. Norcross: How accurate do you think you can be about the varices?

Dr. Hanelin: I think we can be very accurate with a careful examination.

In the films taken on admission a number of small, scattered densities are seen throughout both lungs, chiefly in the upper halves, but there are also a few densities in the left lower lung. Some of the densities, all of which are discrete, are calcified, particularly those in the lower portion of the left lung. In addition, there is a poorly defined density in the region of the right upper lobe, which, in serial films, becomes larger; in other words, an area of consolidation, which originally was small, while followed at intervals for one month, became progressively more extensive. At the end of the month a few new densities also appeared on the left side. Although the process seems to be primarily consolidative, there is probably some element of atelectasis that becomes more marked as we watch it. Within the consolidated lung there are some air-containing areas that may represent abscesses or bronchiectatic cavities. These are particularly well seen in the lateral films. Fluid levels are visible within the right upper lobe anteriorly in later films. In the last two months more spread occurred in the left lung. This subsequently cleared almost completely on the left side. Progressive contraction of the right lung is seen with the trachea drawn toward that side. There may well be some adenopathy around the right hilus. Considerable obvious clearing of the process on the right is evident in the last chest examination, although there is still disease in the partially atelectatic right upper lobe.

Dr. Norcross: How much calcification do you see within the small nodules?

Dr. Hanelin: Some of them are densely calcified,

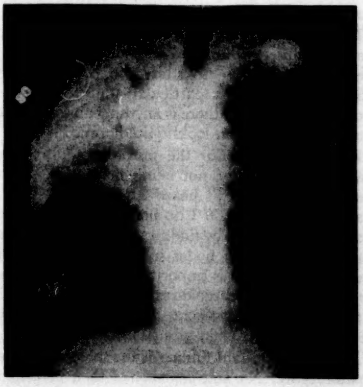

Figure 2.

particularly in the left lower lung. There may also be scattered calcium in the lesions in the upper lung. In other words, the early films suggest old bilateral pulmonary tuberculosis.

Dr. Norcross: Do you have any films of the hands or feet?

Dr. Hanelin: I do not believe that any were taken.

Dr. Norcross: In a situation of widespread disease many conditions come to mind. I think I can discard syphilis. Although some of the findings make me consider Banti's syndrome with hypersplenism, many of the necessary features of that condition are not fulfilled. I am willing to discard carcinoma. I shall also discard brucellosis, for, although it can do bizarre things, I have never seen it give a picture of this sort. I mention histoplasmosis only to dismiss it because with all the examinations that were done the organisms should have been found. Moreover, the negative skin test helps to discard this diagnosis. Histoplasmosis, however, could give most of these findings.

I think, then, I can limit my discussion to lymphomas including lymphatic leukemia, sarcoidosis and tuberculosis. With these in mind I shall review the details of the history. The first complaint was apparently pain and stiffness in the shoulders and some other

*Physician, Lahey Clinic.

joints. That is really a general constitutional symptom that does not help much in the differential diagnosis. The patient lost 25 pounds in weight despite a good appetite and adequate food intake. If that is correct it suggests that the metabolic rate was elevated, which in turn suggests the lymphoma or leukemia group. It would be interesting to know whether he had night sweats or itching, but I must assume that he did not. Constipation was mentioned, but I think it was more important to the patient than to the physician. In relation to this I might ask about the failure of the mucosa of the colon to coat well and the radiologist's statement that small polypoid lesions could not be excluded. Would you comment on that?

DR. HANELIN: In the evacuation films it is true that very little barium clings to the mucosa, so that the best opportunity to study the bowel for small lesions is lost in that particular study. It does not necessarily mean that there is anything abnormal, however. The filled colon looks quite normal.

DR. NORCROSS: For the purpose of discussion I shall pass that up as not being important. Since a "leaking heart valve," heard at one time, was not heard at this admission I do not think that the statement is important. The findings of several, small, nontender shotty lymph nodes in the posterior cervical and axillary regions is important. Such lymph nodes are consistent with sarcoidosis and tuberculosis; when of this size they are less consistent, but they occur with the lymphoma-leukemia group.

The next important finding is the splenomegaly and hepatomegaly. No note is made of their consistence. The hematologic study is of considerable interest. This patient had a severe anemia of a normochromic, slightly microcytic type, associated with a severe neutropenia with a total white-cell count of only 1500. Study of the cells showed a relative increase in the lymphocytes and monocytes. Many transfusions were given during the course of his stay in the hospital. In spite of the fact that the reticulocytes were normal and the Coombs test was negative we must consider as a possible cause of the anemia not only that there was a maturation arrest in production of the cells in the bone marrow but also that there was some degree of hemolysis. I think if the data had been complete in this regard some degree of hemolysis would probably have been demonstrated. Was the sedimentation rate determined?

DR. BERNARD M. JACOBSON: The rate was elevated many times.

DR. NORCROSS: Up to 100 mm. or so?

DR. JACOBSON: It was high.

DR. NORCROSS: That is helpful and is perhaps most consistent with the lymphoma-leukemia group. The sternal bone marrow is interesting. Twenty per cent of the elements were erythroid. It would be helpful to know whether that 20 per cent represented evidence of hyperplasia—that is, whether or not the very young forms were increased. The count of 33 per cent mature lymphocytes as well as the increased monocytes may have represented some contamination with peripheral blood, which may easily occur in sternal-marrow aspirations, or it may have represented the chance puncture of a lymphocytic nodule normally present within the sternal marrow. Since I do not know whether one or several punctures were done I cannot be too dogmatic about the meaning of these unusual findings in the bone marrow. The count of 39 per cent granulocytes, which were almost all myelocytes, probably means a maturation arrest at that level.

There was a reversed albumin-globulin ratio although the globulin was not excessively high. This suggests liver damage. There was also evidence from the cephalin flocculation that the liver function was abnormal. The prothrombin time of 70 per cent, if measured by the method that I believe is used here, would also indicate severe liver dysfunction.

DR. JACOBSON: No, that value is considered within normal limits in this hospital.

DR. NORCROSS: The stools were repeatedly negative for occult blood, suggesting that blood loss was not a factor in the anemia. The skin tests for tuberculosis were negative. Although this does not rule out active tuberculosis it is against that diagnosis. It is notoriously negative in sarcoidosis and usually in the lymphoma group. One of the shotty, nontender axillary lymph nodes was biopsied. It showed only chronic lymphadenitis and fibrosis, which may be found in normal people. Possibly another lymph node might have shown something else. The normal peritoneal surfaces are against a widespread miliary tuberculosis, in which we would expect to find nodules on the peritoneum. The liver biopsy showed slight extramedullary hematopoiesis. This is evidence of stress and strain on the bone marrow. The white plaques on the spleen may have been scars from infarcts or nodules of lymphoma, leukemia, sarcoidosis or tuberculosis. The changes in the heart are of no help in the diagnosis. Cultures of the sputum grew abundant alpha-hemolytic streptococci and various other organisms.

DR. EDGAR B. TAFT: Several sputum cultures also grew out hemolytic *Staph. aureus,* some in abundance.

DR. NORCROSS: One blood culture out of four was positive for *Staph. aureus.* I had thought that this was probably a contaminant, but in view of this additional information perhaps more consideration should be given to a *Staph. aureus* bacteremia. The cytologic examination of the sputum for malignant cells I shall assume to have been negative. There was a severe tracheobronchitis, which can be seen in tuberculosis, in sarcoidosis or in the lymphomas, such as Hodgkin's disease.

The numerous antibacterial medications given were all without benefit. I suppose this may have included antituberculosis drugs. Six hundred r of radiation to the spleen was given in an attempt to improve the obvious hypersplenism. Again, no improvement was noted either clinically or hematologically. This, of

course, does not rule out lymphoma, particularly Hodgkin's disease, or leukemia. I do not know whether the spleen shrank, but I assume that it did not. Cortisone was given for two weeks, and again there was no objective change. I believe the operation on the seventy-third day was a splenectomy, done primarily in the hope that the leukopenia and erythroid abnormality could be improved. Furthermore, it was probably hoped that a definite diagnosis could be made.

With all this information I still have to make a differential diagnosis between the lymphoma-leukemia group, sarcoidosis and tuberculosis. My first choice after studying this protocol was the lymphoma-leukemia group. If it were not for the findings in the bone marrow I should discard leukemia immediately, but I am forced to do so anyway. Tuberculosis, although I am sure it was in the background, did not cause the total picture here. I think I must distinguish between sarcoidosis and one of the lymphomas, such as Hodgkin's disease. It is most unusual in Hodgkin's disease to see the amount of regression and change in the chest that occurred in this case. Such a change, however, is consistent with sarcoidosis with superimposed tuberculosis. The pulmonary changes and the type of lesion shown are more commonly seen in sarcoidosis with tuberculosis than in Hodgkin's disease. From a hematologic point of view, this picture, which is rare in any of these conditions, is seen more commonly in one of the lymphomas, particularly Hodgkin's disease. The episodes of intermittent fever are more common in Hodgkin's lymphoma. Taking everything into consideration, I am going to put sarcoidosis with superimposed tuberculosis as my first choice and Hodgkin's disease as my second.

A PHYSICIAN: Would you consider anything like myelofibrosis?

DR. NORCROSS: I have to go on the evidence that I have been given in the protocol. Myelofibrosis is suggested by the finding of some hematopoietic tissue in the liver, but the bone marrow and the peripheral blood do not suggest it.

DR. LEWIS W. KANE: Do you think that this degree of atelectasis occurs with sarcoidosis when the bronchi are not affected? Do you think the same degree of atelectasis occurs with Hodgkin's disease as with tuberculosis?

DR. NORCROSS: Usually not. At best this is a very unusual picture to explain by one diagnosis.

DR. HANELIN: I should think the consolidative process in the lung would be most unusual for sarcoidosis; I have never seen it. I have seen tuberculosis and consolidation although this case had a much more rapid course than is usually observed.

DR. KANE: Would you not expect the sputum to be positive?

DR. HANELIN: In the presence of cavitation the sputum should be positive.

CLINICAL DIAGNOSIS

?Aleukemic leukemia.
?Lymphoma.
?Carcinoma of lung.
Splenic neutropenia.

DR. JOHN NORCROSS'S DIAGNOSIS

Sarcoidosis with superimposed tuberculosis, with secondary hypersplenism.

ANATOMICAL DIAGNOSES

(Hypersplenism.)
Chronic pneumonitis with fibrosis, right upper and middle lobes.
Acute bacterial endocarditis, with miliary abscesses in myocardium and kidneys and bland infarcts of kidneys.
Bronchopneumonia, moderate.
Pulmonary congestion and edema, severe.
Extramedullary hematopoiesis, liver.

PATHOLOGICAL DISCUSSION

DR. TAFT: Dr. Joseph C. Aub made a note in the chart at one point, "In spite of all the negative tests, I cannot think of anything but tuberculosis that could do this."

The operation, as Dr. Norcross suggested, was a splenectomy. There was considerable reluctance to do this, but there seemed to be no other course open to the physicians that might help the patient. The spleen was removed successfully. It weighed 575 gm. but was not otherwise particularly remarkable grossly except for a few areas of capsular thickening. Microscopical examination revealed congestion of the sinusoids, and in the pulp were many plasma cells, a few other inflammatory cells and much hemosiderin. The lymph follicles were reduced in number and size. Dr. Castleman said that the spleen, aside from the hemosiderosis which was probably the result of the numerous transfusions, showed changes that the late Dr. Tracy B. Mallory ascribed to chronic sepsis, most frequently in association with pyelonephritis. There was no evidence of lymphoma, sarcoidosis or leukemia in the spleen. With this information would you like to suggest any other diagnoses, Dr. Norcross?

DR. NORCROSS: No; there must have been tuberculosis in the background but I do not want to change my opinion and say that the whole picture was on the basis of tuberculosis.

DR. JACOBSON: Before splenectomy, unlike Dr. Norcross, most of us did not believe the same disease affected the spleen and the lungs. Sarcoidosis was not considered seriously, especially after the report of the liver biopsy. My interpretation of the bone marrow was different from that reported in the history. There were few lymphocytes in this cellular marrow, with a myeloerythroid ratio of 2:1. There was considerable

hyperplasia of erythroid elements. The granulocytes consisted largely of myelocytes with a few metamyelocytes—in other words a maturation arrest. There was no evidence of leukemia in the bone marrow. When I saw the patient soon after admission I advised a splenectomy to raise the white-cell count as quickly as possible because it seemed probable that he had severe sepsis to which the bone marrow was not responding normally. Cortisone and radiation were tried, and two months later the spleen was removed. By that time the patient had deteriorated considerably and the white-cell count before splenectomy was 700. About six hours after splenectomy it had risen to 6700; thereafter the white-cell count remained at high levels—approximately 20,000, I think.

Another facet of the history requires amplification. The question arose whether the white tablets that he had been taking for the arthritic pains could have been a toxic drug like butazolidine, which might have depressed the white-cell series. The patient's physician did not know what the medication was; it was taken by the patient on his own initiative.

DR. TAFT: The patient did not do well as Dr. Jacobson has indicated. The sputum cultures continued to grow out a hemolytic *Staph. aureus* that was sensitive only to chloramphenicol and one of the less commonly used antibiotics. On therapy with chloramphenicol the cultures of the sputum began to yield a pure growth of *Pseudomonas aeruginosa* that was sensitive to none of the antibiotics. The patient finally died, approximately two months after splenectomy.

I should mention that the radiologists on several occasions believed that the x-ray findings in the lung probably represented tumor.

DR. HANELIN: Intrabronchial tumor is always a consideration in cases of peripheral consolidation.

DR. TAFT: At autopsy the patient was extremely emaciated. The lungs were voluminous, weighing 2000 gm. The upper lobes, particularly on the right, were very heavy, firm and fibrous. There were many thick-walled cystic areas scattered through the right upper lobe that suggested emphysematous blebs. The left upper lobe was extremely fibrotic at the apex. There were severe congestion and edema of the right lower lobe and the left lung. There were also foci suggestive of bronchopneumonia in the left lung. Microscopically the right upper and middle lobes were almost completely replaced by dense fibrous tissue, with scattered cavities lined by columnar and cuboidal epithelium. There was no acute inflammatory process in this part of the lung at the time of the autopsy — only severe chronic inflammation with infiltration of lymphocytes and macrophages. The fibrosis in the apex of the left upper lobe was nonspecific and, I suppose, may have represented old tuberculosis. There was moderate bronchopneumonia in the remaining lobes.

The heart was normal except for a small area of acute endocarditis beneath the posterior cusp of the mitral valve. Microscopically, this showed acute inflammation and superficial necrosis with many colonies of cocci in the fibrin on the surface. The kidneys contained a few bland infarcts and a few foci of polymorphonuclear infiltration, suggesting that they might have been early abscesses. There were a few small abscesses in the myocardium. These changes were apparently associated with the endocarditis in the left ventricle.

The liver was very large, weighing 2900 gm. It was slightly congested but did not look particularly abnormal grossly. It showed a moderate amount of congestion and a few foci of hematopoiesis. There was no satisfactory explanation for its tremendous size. The splenic vein was occluded by a necrotic thrombus, which extended into the portal vein. The mesenteric veins were not involved. Microscopically, this was a severe purulent thrombophlebitis, which had begun to organize. It seems hard to believe that it had existed for two months after the operation because the organization was not extensive enough. Apparently, it was a terminal or late event associated with the severe generalized sepsis. Interestingly enough, there was a small accessory spleen that was not seen at the time of operation.

DR. ALFRED KRANES: How do you put this chain of events together?

DR. TAFT: Hypersplenism certainly was present clinically although the spleen did not show specific changes microscopically. The history suggests, as Dr. Jacobson remarked, that the sepsis occurred as the result of the hypersplenism rather than the reverse. However, it is possible that the hypersplenism was caused by the chronic pneumonitis. It is known that hypersplenism can be associated with chronic infections like tuberculosis and syphilis. It is not too hard to believe that it might also occur with a nonspecific chronic infection similar to that in this patient. Certainly, the histologic changes in the spleen support this idea. We have no other explanation for the hypersplenism.

CASE 40382

PRESENTATION OF CASE

A thirty-one-year-old man entered the hospital because of a shadow in the lung discovered on roentgenographic examination.

Six years before admission the patient was told that an abnormality was found in a routine x-ray film of the chest, but nothing further was done about it. Four months before admission he was in an automobile accident and was cut in the right submandibular region by flying glass. Roentgenograms of the neck and chest were taken, and an abnormality was noted in the chest film.

There was no history of hemoptysis, chills, fever, pneumonia, dyspnea, or cough, except for a severe

attack of the latter during an episode of measles three years before entry. In the past he had had dysentery, malaria, whooping cough and gonorrhea. He had allegedly lost 3 pounds in weight in the six months before entry. He had fractured some left ribs two years before entry in an automobile accident.

He was born in Guatemala, where he had lived most of his life, but he had also spent some time in South America, the United States and Europe.

Physical examination revealed a well developed man in no distress. There was a red, crusted scar in the right submandibular region. There was no cyanosis or clubbing. The chest moved well bilaterally and showed normal percussion and breath sounds throughout except for a slight increase in breath sounds in the left axilla associated with an increase in vocal fremitus; no adventitious sounds were heard. The heart and abdomen were normal. The prostate was firm and symmetrically enlarged, and the seminal vesicles were indurated.

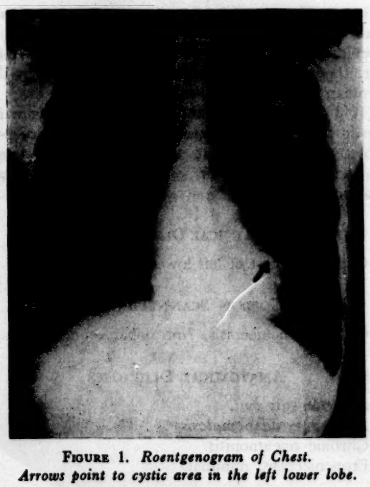

FIGURE 1. *Roentgenogram of Chest.*
Arrows point to cystic area in the left lower lobe.

The temperature was 98.6°F., the pulse 63, and the respirations 18. The blood pressure was 120 systolic, 90 diastolic.

Examination of the blood showed a hemoglobin of 15.8 gm., and a white-cell count of 7900, with 74 per cent neutrophils. The urine (specific gravity of 1.024) was normal. Examination of the sputum was negative for acid-fast bacilli. The vital capacity was 4.2 liters, or 97 per cent of normal. A roentgenogram of the chest demonstrated multiple air-containing cystic cavities lying within the lateral basal segment of the left lower lobe and extending into its superior portion. The largest of these measured more than 4 cm. in greatest diameter (Fig. 1). In addition, there were multiple smaller cavities, a number of strand-like zones of density and thickening of the pleura. There was no appreciable loss of volume in this segment. Several areas of calcification were present in the hilar regions. The right lung was clear. The left sixth rib posteriorly showed notching of its inferior margin. Bronchograms revealed satisfactory filling of the left lower lobe and partial filling of the upper lobe (Fig. 2). Within the lateral basal segment of the left lower lobe a number of

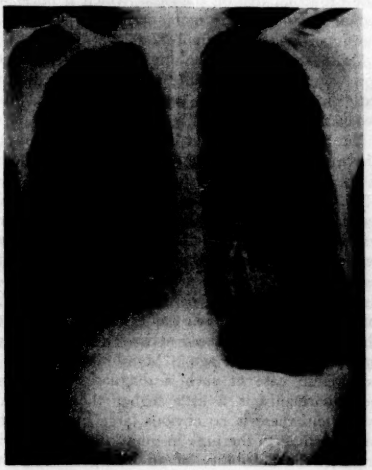

FIGURE 2. *Bronchogram.*
The largest cyst has not been filled with Lipiodol. (There is ectasia of the bronchi lying medial to it.)

dilated saccular bronchi were observed. The large cystic cavities noted on the plain film of the chest were not filled with the radiopaque medium.

On the ninth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. J. GORDON SCANNELL*: Probably no form of clinical or laboratory examination is so likely to turn up an "incidental" finding as the routine chest film. Certainly, many asymptomatic lesions are caught by that screening procedure, and the present case appears to be one of them. Before trying to squeeze clues out of the protocol, may I review the films?

DR. JOSEPH HANELIN: The preliminary films of the chest show the presence of a number of small cystic areas, as well as the larger cavity referred to in the protocol, which lie within the superior por-

*Assistant surgeon, Massachusetts General Hospital.

tion of the lateral basal segment of the left lower lobe. There is some parenchymal reaction about the large cystic zone as well as localized pleural thickening in this region (Fig. 1). The right lung is clear, and the heart is not remarkable.

Bronchograms demonstrate the presence of both cylindrical and saccular bronchiectasis within the lateral basal portion of the left lower lobe; however, none of the medium has entered the largest cystic area (Fig. 2). All the bronchi in the left lower lobe are adequately filled; only the lingual branches of the left upper lobe are demonstrated. The bronchial tree on the right, which is fairly well shown except for the more peripheral branches of the upper lobe, is not unusual.

DR. SCANNELL: In the original report some mention was made of notching of the underside of the sixth rib. Could this have been the result of the injury two years before?

DR. HANELIN: I doubt if it is the result of injury. There is certainly an irregularity of the lower border of the rib, probably developmental in nature.

DR. SCANNELL: I bring up the matter of notching because it suggests that the corresponding intercostal artery may have been enlarged and may have been sending an abnormal branch to the lung in this region. Large systemic arteries to the lung may be associated with cystic changes — a situation that has been called intralobar sequestration of the lung. This subject was discussed at length in one of these exercises a few years ago.† Many of the aspects of the present case fit such a diagnosis except that the abnormality is a little higher than is usually found, and there is no obvious large branch of the aorta running to the area in question; hence my interest in the possibility of an enlarged intercostal artery. This of itself would raise an interesting problem of interpretation — namely, that any area of bronchiectasis may develop a generous collateral blood supply from the systemic circuit. It is possible that this could be considered a congenitally anomalous artery. The presence or absence of other manifestations of infection should help settle this point.

The bronchograms suggest that the abnormal area in the left lower lobe was an integral part of the bronchial tree, although some of the cystic areas were not filled with Lipiodol. The possibility of intralobar sequestration is not ruled out, but the presence of bronchial changes that may have been segmental in nature should alert us to the possibility of an obstructing lesion of a segmental bronchus. It is highly unlikely that an adenoma was present, and on the data given I cannot make this diagnosis. There is the possibility of a retained foreign body, but again historical evidence is lacking.

There is the intriguing possibility that the changes seen may have been the end result of trauma, to which this man seems to have been very susceptible. Old hematomas in the lung may produce radiologic densities that suggest tumor, but I have not heard of their producing the picture of cystic bronchiectasis that is present here.

Cystic bronchiectasis is an interesting problem. The term is a descriptive one, and it is not entirely clear whether cystic bronchiectasis is necessarily an end stage of saccular bronchiectasis, with a great deal of bronchial ectasis and little surrounding parenchymal disease, or whether it may be a congenital defect in a given portion of the bronchial tree. Certainly, in this patient one could not say whether or not a lesion in the bronchial tree was acquired during the attack of measles three years before, or whether the pulmonary changes antedated that episode. In any event, he certainly did not have the history that we ordinarily associate with saccular bronchiectasis or bronchiectasis following lung abscess.

When there are cystic changes in the lung we must think of exotic forms of cysts — hydatid and others. The changes here do not conform to such parasitic cysts, nor do they suggest the cavities of coccidioidomycosis or histoplasmosis. For that matter, they do not suggest tuberculosis, although this protean disease must always be considered.

If I have to make a diagnosis, I shall vote for cystic bronchiectasis, cause unknown, but very possibly associated with an abnormal systemic artery to the lung — in other words, intralobar sequestration.

CLINICAL DIAGNOSIS

Congenital cyst of left lower lobe of lung.

DR. J. GORDON SCANNELL'S DIAGNOSIS

Cystic bronchiectasis, ?intralobar sequestration.

ANATOMICAL DIAGNOSES

Bronchogenic cyst.
Pulmonary adenomatosis.
Chronic pneumonitis.
Bronchiectasis, minimal.

PATHOLOGICAL DISCUSSION

DR. WINFIELD S. MORGAN: Dr. Sweet, will you tell us what you found at operation?

DR. RICHARD H. SWEET: A standard thoracotomy incision was made on the left side, with resection of the seventh rib. There were dense inflammatory adhesions between the cyst-bearing portion of the lobe, which seemed to be one of the inferior segments, and the adjacent surface of the chest wall. Several calcified lymph nodes were present in the hilar area, and there was a puckered scar at the apex of the lung that suggested an old healed tuberculous in-

†Case Records of the Massachusetts General Hospital (Case 36361). *New Eng. J. Med.* 243:383-387, 1950.

fection. The dissection of the lobe was not unusually difficult. The arterial supply to the superior

FIGURE 3.

segment of the lower lobe consisted of two separate branches. The remainder of the vascular pattern was normal, and no systemic artery could be discovered. The bronchial vessels, on the other hand, were rather large, as is characteristic with an inflammatory lesion of this sort. The venous pattern, however, was rather peculiar in that there were many branches from the lingula area crossing the septum into the lower portion, and it appeared as though some of the arterial supply to the upper lobe was anomalous. This did not interfere with dissection of the lower lobe. The upper lobe in this patient was unusually large.

DR. MORGAN: On section of the specimen a single multiloculated cyst, measuring 5 cm. in greatest dimension, was encountered within the lateral basal segment (Fig. 3). Although the surrounding bronchi were slightly ectatic, the appearance was more in keeping with a bronchogenic cyst than with true cystic bronchiectasis. Microscopically, the cyst was lined by bronchial epithelium. As one can see from the photograph, there was considerable gray-white, rather firm tissue about the cyst, and microscopically this revealed an unexpected but striking histologic picture. The alveoli and respiratory bronchioles were lined by a uniform layer of tall columnar goblet cells often forming papillary tufts. Other alveoli were lined by cuboidal epithelium with sharp transition to the goblet cells. Macrophages and mucin filled many of the alveolar spaces. This process was limited to the areas surrounding the cyst and was indistinguishable from the so-called pulmonary adenomatosis; it did not resemble in any way the metaplastic alveolar epithelization so often seen in chronic pneumonitis.

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MORTALITY FROM SNAKEBITE

THE Inter-Governmental Conference of the League of Nations suggested in 1935 that the Health Organization of the League study the matter of standardization of antivenins. A study was actually made of the antiserums against the venoms of European vipers; one thing failing to lead to another, the matter rested there until more recently, when the World Health Organization raised the question whether snakebite mortality was of sufficient importance to merit consideration by that august body.

A new study was consequently put on foot, which resulted in a comprehensive report by S. Swaroop, chief of the Statistical Studies Section of the World Health Organization, and B. Grab, of the Section, published early this year in the *Bulletin of the World Health Organization*.* If snakes have the faculty of fascinating certain of their victims, then this almost monumental report on the prevalence and distribution of snakebite must exercise the same influence over many of its readers.

The researches of Swaroop and Grab are obviously handicapped by the fact that registration of deaths in general is inadequate in many areas, and that mortal snakebites in particular are most prevalent in underdeveloped countries, presumably reaching their peak in the most remote sections of those countries.

Herpetologists have long whiled away their time with the classification of serpents and investigations into their distribution and habits. Some 2500 varieties of snakes are recognized, which are divided into 13 families; less than 200 varieties are dangerous to man. These are found mainly in 4 families: the Elapidae, including the cobras of the Old World and the coral snakes of the New; the Viperidae, found in the Old World only; the Crotalidae, of the New World and Asia, including the "pit vipers," and the Colubridae, of which the rear-fanged venomous varieties are found almost exclusively in Africa. Most of the harmless snakes are also colubrids. A fifth family, the Hydridae, contains the relatively few venomous sea snakes inhabiting the coastal waters of southern Asia and northern Australia. A species that may have made an ocean crossing disports itself off the west coast of Central America.

Although venomous snakes are rarely found in cold climates a "robust" viper occurs in Siberia and in Scandinavia to within the Arctic Circle. In North America poisonous snakes are found infrequently in Canada; they do not occur at all in the Azores, the Canary and Cape Verde Islands, most of the West Indies, Ireland, Iceland and the Orkney and Shetland Islands.

Various pit vipers from the family Crotalidae are found in the United States—the true rattlesnake, the pigmy rattler or massasauga, the copperhead and the cottonmouth, and the highly venomous coral snake

*Swaroop, S., and Grab, B. Snakebite mortality in world. *Bull. WHO* 10:35-76, 1954.

from the Elapidae. Two occur in New England, the copperhead, which is not found north of central Massachusetts, and the timber rattler. The water moccasin, or cottonmouth, the prairie rattler and the diamondback rattler cause 95 per cent of the deaths, the western diamondback being responsible for twice as many fatalities as its eastern counterpart. On an average 56 deaths occur each year in the United States "due to poisoning by venomous animals," a category that includes the arachnids and insects as well as the reptiles. This mortality and its allocation varies greatly among the states; in Arizona over a period of twenty-five years almost twice as many deaths have resulted from scorpion bites as from snakebites and insectbites combined. In all Canada during a period of five years only 10 deaths were attributed to "venomous animals."

The only poisonous snakes found in Europe are the true vipers, and of these only the common or northern viper, or adder, inhabits Great Britain. Over a period of five years the average annual mortality in England and Wales from all venomous animals was only 8; it was 0.2 in Scotland, and thanks to St. Patrick, 0 in Ireland. Since only 7 deaths actually from adderbite have been reported in England and Wales in fifty years it seems apparent that St. Patrick, whatever his intent, was unable to herd the traditional reptiles of Hibernia across St. George's Channel.

Since the prevalence of mortal snakebite in Africa can hardly be even guessed at, the countries of southern Asia are accepted as those in which the prevalence is greatest. Thus, in India, prior to partition, 15,000 a year occurred, or about 5.4 per 100,000 population. The highest mortality rate occurs in Burma, however, where over 2000 deaths per year constitute a rate of 15.4 per 100,000 population. All in all the world's total snakebite deaths are estimated at 30,000 to 40,000 annually, excluding certain central European countries, China and the United Soviet States of Russia, where possibly snakebite goes unrecognized.

The fatality rate for bitten persons in a specific study made in India was 17.9 per cent, varying from 4.8 per cent for persons bitten by cobras to 88.9 per cent for the victims of krait bites. Apparently, there are various instrumentalities that are sharper than a serpent's tooth.

MEDICAL-CARE SURVEY

THE announcement of a research grant to United Community Services from the Public Health Service started a series of efforts to improve and make better use of medical care in metropolitan Boston. Although all are proud of its achievements and the recognition that this area has received as a medical center, room for improvement undoubtedly exists.

To improve the quality and increase the availability and more effective utilization of medical care, United Community Services, through its health division, proposes to develop a regionalization of facilities in an urban area — namely, metropolitan Boston. The objectives of the program are to encourage better working relations between medical-care units, such as hospitals and clinics, and other facilities; to define more clearly the roles of hospitals, health departments and voluntary agencies in the prevention of disease and the maintenance of health; and to improve the usefulness of the medical-care facilities for education in medicine and related fields.

None of these aims are radical innovations; this fact does not make them less worthy. Particularly challenging is the complexity of the medical-care facilities in Boston and the great variety of organizations operating them. As in most metropolitan areas the diversity is matched by the range in quality of service — from extremely good to somewhat less than fair. An asset is the spirit of co-operation among hospitals, medical schools and public-health agencies. The area is fortunate in the number of outstanding physicians and other leaders in medical care available to help in such a plan.

An early responsibility of the project is the development of tools of measurement. This is necessary to establish a base line and to evaluate changes brought about by the plan. The purpose of the research grant from the Public Health Service is to develop and test such methods of assessing quality, availability and utilization of medical care and public-health facilities. The program will be conducted before, and then concurrently with, the regionalization effort of the Health Division of United Community Services.

DR. ALTON POPE RETIRES

THIS week friends and associates of Dr. Alton S. Pope meet to pay tribute to him, signifying his retirement from the Massachusetts Department of Public Health. The *Journal* takes this opportunity to add its voice in appreciation of Dr. Pope's twenty-four years of public service.

A graduate of Tufts College Medical School and Harvard School of Public Health, Dr. Pope joined the Massachusetts Department of Public Health in 1929 as director of the Division of Tuberculosis. For the next twenty-four years he administered the tuberculosis program of the State; this involved general supervision of the state tuberculosis sanatoriums, the clinic program, state-directed mass roentgenographic services and other activities such as the Pondville and Westfield cancer hospitals and the poliomyelitis-orthopedic services at Lakeville State Sanatorium. In 1937 he became deputy commissioner of the Massachusetts Department of Public Health, a post that he held until his retirement this summer and filled in addition to his work in tuberculosis.

It is perhaps in this capacity that he has rendered his greatest service to the citizens of the Commonwealth. Under a series of state administrations and in association with four successive commissioners of public health, it was he who provided the continuity, the intimate knowledge of the department and of state administration in general that helped to keep this organization in its position of leadership. At many times obstacles arose that might have seriously impeded his work: budget cuts, shortages of personnel—especially those of World War II—and the threat of political interference with professional activities. Through all these vicissitudes Dr. Pope has provided a much needed stabilizing influence. He has quietly fought for the maintenance of high standards; his good judgment has guided the Department in many ventures into new fields and ensured that new programs were set up on a sound basis, while not permitting the neglect of important long-established activities. The confidence in which he is held by various official and voluntary health agencies and members of the medical profession has been of distinct aid to the Department on many occasions. However, his innate modesty and avoidance of fanfare have made him less well known to the public than his achievements have warranted.

Along with his official services on behalf of the people of the Commonwealth Dr. Pope has found time to write, in collaboration with Dr. Henry D. Chadwick, a small but important textbook, *The Modern Attack on Tuberculosis*, as well as a number of papers most of which deal with the epidemiology of this disease. He has served in the councils of both the American Public Health Association and the National Tuberculosis Association and was president of the latter organization in 1951-52. He has also held faculty appointments in the Department of Preventive Medicine at Tufts College Medical School and the Department of Public Health Practice of Harvard School of Public Health during most of his years in Boston. He now joins the latter school on a full-time basis, to participate in the teaching program of the Department of Epidemiology. It was in this field that he received the degree of Dr. P. H. twenty years ago.

MANUAL OF THE MASSACHUSETTS MEDICAL SOCIETY

THOSE of the *Journal's* readers who are members of the Massachusetts Medical Society—and possibly, although not probably, countless others—will find matters of absorbing interest in the new *Manual* prepared and distributed by the home office. This larger manual replaces the smaller familiar *Digest, By-Laws, Code of Ethics, Publicity Code and Medical Defense Act of the Massachusetts Medical Society and the Principles of Medical Ethics of the American Medical Association,* —containing all this and much more, too.

Herein will be found, in proper heraldic language, a description of the seal adopted by the Society on April 9, 1783, which "displays a Figure of Aesculapius in his proper Habit pointing to a wounded Hart nipping the Herb proper for his Cure, with the Motto *Natura duce.*" A brief account of the founding and development of the Society follows and a section of questions and answers pertinent to its functions and the obligations of its fellows. Other paragraphs describe and explain various of the Society's traditions and activities.

The remainder of the *Manual* is made up largely of the official documents contained in the original pamphlet; it is being distributed to all fellows of the Society.

As society in general moves forward or onward, or in whatever direction it moves, its various relations seem always to become more complicated. So it is with societies in particular, including the Massachusetts Medical Society. The new manual, on the preparation of which the Secretary is to be congratulated, brings together under one cover simple and satisfactory expositions of the more chronic of these complexities.

The Glen Haven, N. Y. Water Cure Establishment was destroyed by fire on the 13th inst. The patients (the papers say) passed an unusual quantity of water, *and prevented the entire destruction of the building.*

Boston M. & S. J., *Sept. 27, 1854*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

REMICK — Sumner H. Remick, M.D., of Ashburnham, died on August 18. He was in his sixty-eighth year.

Dr. Remick received his degree from Tufts College Medical School in 1912. He was formerly superintendent, Middlesex County Sanatorium and vice-president, Massachusetts Medical Society. He was a fellow of the American Medical Association, a member of the American Trudeau Society, Massachusetts Trudeau Society, Massachusetts Tuberculosis and Health League, Middlesex Health Association, Massachusetts Public Health Association and the Ashburnham Board of Health and a director of the Boston School of Occupational Therapy.

He is survived by three daughters and seven grandchildren.

TAYLOR — Lewis Taylor, M.D., of South Deerfield, died on August 12. He was in his sixty-eighth year.

Dr. Taylor received his degree from Middlesex College of Medicine and Surgery.

He is survived by his widow, two sons and a daughter.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Grenzen des Normalen und Anfänge des Pathologischen im Röntgenbilde des Skelettes. By Prof. Dr. A. Köhler. Edited by Dozent Dr. E. A. Zimmer, Bern/Fribourg. Ninth edition. 8°, cloth, 672 pp., with 1282 illustrations. Stuttgart: Georg Thieme, 1953. DM 88. (Distributed by Grune and Stratton, New York.)

The first edition of this authoritative book on the roentgenology of the skeletal system was published in 1910, the eighth being issued in 1943. This new edition has been completely revised, both in text and in illustrations. Originally written by Dr. Köhler and continued by Dr. Zimmer, the book has been translated into English, French, Italian and Spanish. The text is divided into six main categories: general and special considerations; upper extremity; shoulder, thorax and ribs; skull; spine and pelvis; and lower extremity. The references, about 3000, are carried as footnotes to the pages. There is a good index, and the publishing is excellent. The book should be in all collections on the subject.

Viruserkrankungen des Menschen: Ein Lehrbuch der Klinik, Epidemiologie und Ätiologie der menschlichen Virosen. By Dr. Med. W. D. Germer, chief physician of the medical clinic and lecturer, Universität Tübingen. 8°, cloth, 190 pp., with 47 illustrations. Stuttgart: Georg Thieme, 1954. DM 30. $7.75. (Distributed by Intercontinental Medical Book Corporation, New York.)

Dr. Germer has written a monograph on the etiology, epidemiology and clinical appearance of the virus diseases of man. The text presents the subject in 8 parts: virus diseases of the respiratory tract, liver, central nervous system, muscles, lymph nodes, eye and skin and infectious diseases due directly to a virus. The appendixes consist of tables of incubation, isolation and quarantine times, laboratory diagnosis and coloring methods. The literature is surveyed, and lists of references are appended to the chapters. There is a good index, and the publishing is excellent.

Lehrbuch der klinischen Hämatologie. By Prof. Dr. Hans Schulten, Köln. Fifth edition. 8°, cloth, 516 pp., with 82 illustrations. Stuttgart: Georg Thieme, 1953. DM 54. (Distributed by Grune and Stratton, New York.)

This new edition of a book on clinical hematology has been revised and brought up to date, incorporating the advances in the subject of the last ten years. The material is divided into chapters on anatomy and physiology, methods, pathology of the erythrocytes, the anemias, special diseases such as polycythemia and hemachromatosis, pathology of leukocytes, hemorrhagic diseases, panmyelopathy, diseases of the reticuloendothelial system and appearance of the blood in various diseases. Short lists of references are appended to the chapters, and the index is good. The book should be in all collections on the blood.

Die Mund- und Rachenkrankheiten, Klinik und Therapie: Ein Leitfaden für Ärzte und Studierende. By Prof. Dr. C. R. Griebel, Bad Nauheim. 8°, cloth, 140 pp., with 42 illustrations. Stuttgart: Georg Thieme, 1954. DM 29. $6.90. (Distributed by Intercontinental Medical Book Corporation, New York.)

This manual on diseases of the mouth and pharynx and their treatment is written for students and physicians. The material is in 2 sections: general and clinical. The former considers briefly anatomy and topography, flora of the mouth, physiology, methods of study and symptomatology. The latter discusses, in order, tumors, foreign bodies, mechanical, chemical and thermic changes, odontogenic inflammations, inflammation of the mucous membrane, diseases of the salivary glands, tongue and lips, inflammation of the fauces, internal diseases and the mouth, nerve diseases and the mouth, foetor ex ore, disturbances of speech caused by anomalies of the mouth and pharynx and differential diagnosis of bleeding from the mouth and pharynx. Extensive bibliographies are appended to the chapters, and there is a good index.

Lehrbuch der Haut- und Geschlechtskrankheiten. By Dr. Walther Schönfeld, professor and director, Universitätsklinik und Poliklinik für Haut- und Geschlechtskrankheiten in Heidelberg. Sixth edition. 8°, cloth, 480 pp., with 217 illustrations and 16 colored plates. Stuttgart: Georg Thieme, 1953. DM 36. (Distributed by Grune and Stratton, New York.)

This standard German textbook, first published in 1938, has been revised. The text is presented in 2 parts: dermatology and sexual diseases. Dermatology is treated according to etiology and site of the lesions. The second part is devoted to a comprehensive consideration of syphilis and gonorrhea, with emphasis on treatment. There is an index of authors and subjects. Seven color plates are placed at the back of the book. The volume should be in all collections on the subjects.

Die Bedeutung des Blutchemismus: Besonders in Beziehung zu Tumorbildung und Tumorabbau. (Der Zell- und Gewebsstoffwechsel als innere Krankheitsbedingung II Teil.) By Prof. Dr. Ernst Leupold, director, Pathologischen Institut der Universität Köln. 8°, cloth, 207 pp., with 102 illustrations and 116 tables. Stuttgart: Georg Thieme, 1954. DM 48. $11.40. (Distributed by Intercontinental Medical Book Corporation, New York.)

This special monograph discusses the importance of blood chemistry in relation to tumor formation. The introduction, which deals with the blood system, blood lipoids and sugar, the cholesterol and phosphatide system and the cholesterol, sugar and phosphatide system, is followed by chapters on pathology, proliferative processes, tumor formation, the importance of blood sugar and cholesterol ester, the time factor, nonmalignant tumors and dermatoses and therapy. The final chapter is a summary of the subject. A subject index concludes the text. The monograph should be in all collections on blood and tumors.

Lehrbuch der Gynäkologie. By Prof. Dr. Med. Heinrich Martius, director, Universität-Frauenklinik Göttingen. With diagrams by Käthe Droysen. Third edition. 8°, cloth, 414 pp., with 446 illustrations. Stuttgart: Georg Thieme, 1953. DM 49.80. (Distributed by Grune and Stratton, New York.)

In this new edition a standard German textbook on gynecology first published in 1946 has been revised and brought up to date. There are chapters of unusual interest on sterility and the prevention of conception, gynecologic urology and orthopedics. There is a good index, and the publishing is excellent.

Die objektive Stereoskopie an Röntgenbildern: Eine diagnostische Methode. By Prof. Dr. A. Hasselwander, Arlaching/Chiemsee. 8°, cloth, 187 pp., with 125 illustrations. Stuttgart: Georg Thieme, 1954. DM 27. $6.40. (Distributed by Intercontinental Medical Book Corporation, New York.)

This monograph describes and reviews the literature on objective stereoscopy in roentgenology. The general part is concerned with the importance of procedure and technics. The second part deals with diagnosis. The first chapter, on anatomy and physiology, is followed by those on orthopedics, gynecology, dentistry, internal medicine and surgery. There is an atlas on frozen sections of 27 pages. There is a bibliography of 7 pages and an excellent index.

Medizin in Bewegung: Klinische Erkenntnisse und ärztliche Aufgabe. By Dr. Med. Richard Siebeck, professor of internal medicine, Universität Heidelberg. Second edition. 8°, cloth, 496 pp. Stuttgart: Georg Thieme, 1953. DM 33. $7.85. (Distributed by Intercontinental Medical Book Corporation, New York.)

The subject of this volume, medicine in motion, is interesting. The book, which discusses the latest knowledge on a number of medical subjects, was first published in 1949. This new edition has been revised. The chapters concern the

basis of medical knowledge; disease and personality (stomach ulcers); the vegetative system—thyrotoxicosis and Basedow's disease; disorders of metabolism—diabetes insipidus and mellitus, obesity and loss of weight; reaction to foreign substances—allergy and bronchial asthma; acute infections—rheumatism of the joints, typhoid and paratyphoid fever, bacillary dysentery, lung inflammation; chronic infections—tuberculosis of the lung; heart and circulation; high blood pressure; Bright's disease; disease and death—cancer of the stomach; psychosomatic pathogenesis—neurotic reactions; social pathogenesis—social medicine and insurance; basis for judgment; and treatment of the sick. There is a comprehensive index, and the publishing is excellent. This unusual and interesting book should be in collections on medicine.

Das geburtshilfliche Gutachten im Vaterschaftsprozess: Darstellung der Grundlagen, der Technik und der Stellung im Prozess für Mediziner, Juristen und Beamte der Jugendämter. By Prof. Dr. Med. Kurt Podleschka, chief physician, Universität-Frauenklinik Erlangen. 8°, cloth, 237 pp., with 64 illustrations and tables. Stuttgart: Georg Thieme, 1954. DM 33. $7.85. (Distributed by Intercontinental Medical Book Corporation, New York.)

In this monograph the author discusses the legal opinions of fatherhood from an obstetric point of view. The subject is comprehensively covered, and there is a bibliography of 12 pages. The lack of an index is noted. The book should be in collections on legal and social medicine.

Thoughts About Life. By Felix Friedberg. 8°, cloth, 40 pp. New York: Philosophical Library, 1954. $2.50.

In 5 short essays a college teacher presents his point of view on such subjects as ideation or reality, the function of a university, philosophy's service to the scientist and characteristic phenomena of living things.

Present Knowledge in Nutrition: Prepared from articles published in the Journal, Nutrition Reviews. Revised and edited by the Editorial Staff and Advisory Board. 4°, paper, 122 pp. New York: Nutrition Foundation, Incorporated, 1953.

This summary presents the latest knowledge on nutritional agents, the minerals and the vitamins.

Antiseptics, Disinfectants, Fungicides, and Chemical and Physical Sterilization. Edited by George F. Reddish, Ph.D., Sc.D.(Hon.), St. Louis College of Pharmacy and Allied Sciences, and Lambert Pharmacal Company, St. Louis, Missouri. 8°, cloth, 841 pp., with 71 illustrations and 130 tables. Philadelphia: Lea and Febiger, 1954. $15.00.

This valuable composite book is the combined work of 30 authorities on their subjects. The text begins with a historical review and a definition of terms by the editor. Then follow in order methods of testing of antimicrobial agents in detail for the various groups — antiseptics, disinfectants, fungistats and fungicides, preservatives, chemical and physical sterilization, and pasteurization. The pertinent literature is evaluated, and lists of references are appended to the chapters. There are indexes of authors and subjects, and the publishing is excellent. The book is recommended for all medical libraries and for collections on public health.

Surgery. Edited by Sir Zachary Cope, B.A., M.D., M.S., F.R.C.S. 8°, 772 pp., with illustrations. London: Her Majesty's Stationery Office, 1953. 80s. net. *(Medical History of the Second World War.)*

This volume on surgery chronicles the advances in surgery made during World War II. The text is kept within the scope of a single volume by the omission of common material usually found in all textbooks. The whole field of surgery is covered, including blast and crush syndrome, immersion (trench) foot, physiotherapy and rehabilitation, nonpulmonary tuberculosis, traumatic effects of the atomic bomb and surgery in prisoner-of-war camps. Lists of references are appended to the chapters. There are indexes of authors and subjects, and the publishing is excellent.

Medical Progress. A review of medical advances during 1953. Morris Fishbein, M.D., Editor. 8°, cloth, 345 pp. New York: Blakiston Company, 1954. $5.00.

This second volume in a series of practical essays covers the various specialties written by 28 authorities in their particular fields. Boston physicians are well represented by Drs. Paul D. White (cardiology and heart disease), Stanley Gershoff and Fredrick J. Stare (nutrition), Lewis M. Hurxthal (endocrinology) and Frank R. Ober (orthopedic surgery). The various articles give a comprehensive summary of the advances during 1953. Extensive bibliographies are appended to the chapters, and there is a good index. The series should be in all medical libraries.

Understanding the Japanese Mind. By James Clark Maloney, M.D. 8°, cloth, 252 pp. New York: Philosophical Library, 1954. $3.50.

Dr. Maloney discusses the psychoanalysis of the Japanese as compared with that of the Western world.

Transactions of the American Goiter Association: 1953 annual session, May 7, 8 and 9, Chicago, Illinois. 4°, cloth, 423 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1954. $13.50.

The *Transactions* of the association contain all the papers read at the annual meeting. The presidential address, entitled "Controversial Thyroid Problems," by Dr. Claude J. Hunt and the Van Meter Prize Essay, on the subject "The Thyroidal Uptake of Stable Iodine Compared with the Serum Concentration of Protein-Bound Iodine in Normal Subjects and in Patients with Thyroid Disease," by Drs. Belton A. Burrows and Joseph F. Ross, are published in full. The set should be in all medical libraries.

The Billroth I Gastric Resection, with Particular Reference to the Surgery of Peptic Ulcer. By Horace G. Moore, Jr., M.D., Wilmington, North Carolina, formerly, instructor in surgery, University of Washington School of Medicine, and chief resident in surgery, King County Hospital, Seattle; and Henry N. Harkins, M.D., Ph.D., F.A.C.S., professor of surgery and executive officer of the department of surgery, University of Washington School of Medicine, surgeon-in-chief, King County Hospital, Seattle, and formerly, professor of surgery, Johns Hopkins University School of Medicine. With a foreword by Dr. Gösta Bohmansson, professor and surgeon-in-chief, emeritus, Central Hospital, Orebrö, Sweden, and a preface by Dr. John M. Waugh, head of a section in the division of surgery, Mayo Clinic, and professor of surgery, Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota. 4°, cloth, 175 pp., with illustrations. Boston: Little Brown and Company, 1954. $7.50.

The authors of this comprehensive monograph have made a thorough study of the Billroth I operation. They have surveyed the literature and compared the relative merits of this operation with those of the Billroth II procedure. Their conclusions are based on a consecutive series of 140 Billroth I gastric resections performed from January 1, 1948, to October 31, 1952. Their total experience to December 1, 1953, consisted of 274 operations, and they conclude that the Billroth I procedure has certain advantages over the Billroth II procedure. There is a bibliography of 15 large quarto pages and indexes of authors and subjects. The publishing is excellent. The book should be in all medical libraries and available to all surgeons and gastroenterologists.

Nuova idea del male contagioso de' buoi. By Carlo Francesco Cogrossi. Reproduced in facsimile with an introduction by Luigi Belloni and translated into English by Dorothy M. Schullian. *(Edita dalla Sezione Lombarda della Società Italiana di Microbiologia pel VI Congresso Internazionale di Microbiologia — Roma, 6-12/IX/1953.)* 16°, paper, 119 pp., with illustrations. 1953. Free of charge.

In the summer of 1711 an epizootic, a plague among oxen, was imported into Italy and continued its ravages throughout the country. In 1714, in Milan, Carlo Francesco Cogrossi wrote his *Nuova idea del male contagioso de' buoi* addressed to Antonio Vallisnieri. The original text is reproduced in facsimile with a free translation into English.

The Dynamics of Virus and Rickettsial Infections: International symposium. Edited by Frank W. Hartman, M.D., Frank L. Horsfall, Jr., M.D., and John G. Kidd, M.D. 8°, cloth, 461 pp., with illustrations. New York: Blakiston Company, 1954. $7.50.

At this symposium, held in Detroit in October, 1953, authorities from the United States and abroad read and discussed the various papers, which were divided into 5 main divisions: mechanisms; ecology and pathogenesis; immunity, laboratory diagnosis; and approaches to prophylaxis and therapy. Lists of references are appended to the 32 chapters and the publishing is good. The lack of an index is noted. This is the type of book that should be in all medical libraries.

The Mechanism of Inflammation: An international symposium. Edited by G. Jasmin, M.D., and A. Robert, M.D., Institut de Médecine et de Chirurgie Expérimentales, Université de Montréal. 8°, cloth, 308 pp., with illustrations. Montreal: Acta, Incorporated, 1953. $8.50.

This symposium was truly international in scope, with 40 persons from the United States and Canada, Europe and the East being represented. The text is divided into 4 parts: general considerations; morphology; and chemistry and hyperergic inflammations (histamines, antihistamines, and so forth). There are extensive indexes of authors and subjects, and the publishing is excellent. This type of book should be in all medical libraries.

Psychosomatic Case Book. By Roy R. Grinker, M.D., director, Institute for Psychosomatic and Psychiatric Research and Training of the Michael Reese Hospital, and clinical professor of psychiatry, University of Illinois, College of Medicine; and Fred P. Robbins, M.D., associate psychiatrist, Michael Reese Hospital, and staff member, Chicago Institute for Psychoanalysis. 8°, cloth, 346 pp. New York: Blakiston Company, 1954. $6.50.

The authors present a series of 79 cases illustrating the psychosomatic approach to common diseases of the various systems of the body and discuss diagnosis, special syndromes and therapeutics. Lists of references are appended to the chapters; there is a general bibliography and a good index.

The Vitamins in Medicine. By Franklin Bicknell, D.M., M.R.C.P., honorary physician, French Hospital, London; and Frederick Prescott, M.Sc., Ph.D., F.R.I.C., M.R.C.P., clinical research director, Wellcome Foundation, London. Third edition. 8°, cloth, 784 pp., with 245 illustrations. New York: Grune and Stratton, 1953. $13.00.

This standard British reference book was first published in 1942, and the second edition of 1946 required 2 reprintings. This new edition has been thoroughly revised and mostly rewritten. Extensive lists of references are appended to the chapters, and the number of titles has been increased from about 4500 to 5500. There is a good index, and the publishing is excellent. The book should be in all medical libraries.

Bibliography of Occupational Health: Occupational health and related publications from the Public Health Service. 1909-1953. By Frances L. Hyslop, B.A.; and W. M. Gafafer, D.Sc. 8°, paper. 110 pp. United States Department of Health, Education and Welfare, Public Health Service, Division of Occupational Health of the Bureau of State Services. (Publication No. 9, *Public Health Bibliography Series.)* Washington: Government Printing Office, 1954. 35 cents.

This bibliography lists 1938 titles issued under the auspices of the United States Public Health Service. The material is divided into 14 sections; there is a good index and a list of publications of the Public Health Service.

Carcinoma of the Colon. By Leland S. McKittrick, M.D., clinical professor of surgery, Harvard Medical School, surgeon-in-chief, New England Deaconess Hospital, consulting visiting surgeon, Masachusetts General Hospital, and consultant in surgery, Peter Bent Brigham Hospital; and Frank C. Wheelock, Jr., M.D., assistant in surgery, Massachusetts General Hospital, and assistant in surgery, Harvard Medical School. 8°, cloth, 94 pp., with 12 illustrations and 8 tables. Springfield: Charles C Thomas, 1954. $3.25. (Publication No. 189, *American Lecture Series.)*

The authors discuss the etiology, prevention, diagnosis, pathology, anatomy and treatment of carcinoma of the colon and benign adenomatous polyps. Two thirds of the text is devoted to surgery — preoperative, operative and postoperative. Statistics for the ten years, 1942-1952 (207 cases), show that the mortality was 5.3 per cent. There is a bibliography of 34 references and a good index.

Roentgenographic Technique: A manual for physicians, students and technicians. By Darmon Artelle Rhinehart, A.M., M.D., F.A.C.R., professor emeritus of anatomy and roentgenology, University of Arkansas, honorary member, American Society of X-Ray Technicians, honorary registered x-ray technician, and roentgenologist, St. Vincent's Infirmary and the Missouri Pacific Hospitals, Little Rock, Arkansas. Fourth edition. 8°, cloth, 454 pp., with 216 figures and 18 tables. Philadelphia, Pennsylvania: Lea and Febiger, 1954. $8.50.

The author has thoroughly revised the text of the new edition of his well known special book to bring it up to date, and considerable material has been added. The illustrations have been increased and in some instances changed. Some of the technical procedures that require expensive apparatus, such as kymography, cardiography, body-section roentgenography and cerebral angiography, have been omitted. Lists of references are appended to the chapters; there is a good index, and the publishing is excellent.

Rorschach Responses in Old Age. By Louise Bates Ames, Ph.D., director of research, Gesell Institute of Child Development, and member of the Society for Projective Techniques and the Rorschach Institute, Incorporated; Janet Learned, Ph.D., director of preschool service; Ruth W. Métraux, M.A., formerly Rorschach specialist, Gesell Institute; and Richard N. Walker, M.A., research assistant. 8°, cloth, 229 pp., with 44 tables. New York: Paul B. Hoeber, Incorporated, 1954. $6.75.

The authors present the results of a Rorschach study of a large group of persons between the ages of seventy and a hundred years. The same authors previously studied and published responses in children, and now offer the opportunity for the first time of comparing the old person with the child. There are a short bibliography and an index.

You and Your Health. By Edwin P. Jordan, M.D., executive director, American Association of Medical Clinics. 8°, cloth, 296 pp. New York: G. P. Putnam's Sons, 1954. $3.95.

Dr. Jordan has gathered together in this volume a selection of his syndicated newspaper articles on health problems. They are written in an informal style and are divided into 8 categories: the heart, blood pressure and hardening of the arteries; the digestive system, including cancer and related disorders; infections; skin, hair, and nails; rheumatism, arthritis and allied disorders; allergies; eyes and vision; and the ears and hearing. An index has been provided, and the publishing is good.

Modern Medicine Annual 1954: An annual volume containing the articles that appeared in the twenty-four issues of Modern Medicine *during 1953,* 8°, cloth, 1454 pp., with illustrations. Minneapolis, Minnesota: Modern Medicine, 1954. Free.

This volume contains the articles that were published in *Modern Medicine* during 1953. They have been rearranged according to classes, and there are indexes of subjects and authors, making the material easily available for reference purposes.

Proceedings of the Annual Meeting, Council for High Blood Pressure Research, American Heart Association. Cleveland, Ohio, May 15-16, 1953. Vol. 2. 8°, cloth, 96 pp. New York: American Heart Association, 1954. $2.00.

Five papers were presented at this second meeting of the Council. The subjects discussed were the anterior pituitary gland and adrenal cortex in experimental hypertension; the role of renin in experimental hypertensive vascular diseases; salt-water balance and blood pressure; changing patterns of sodium metabolism in hypertension; and electrolyte participation in human hypertension.

NOTICES

AMERICAN TRUDEAU SOCIETY

The Eastern Section meeting of the American Trudeau Society will be held at the Sheraton Park Hotel, Washington, D.C., October 22 and 23. Recent advances in chemotherapy, surgical procedures and results of investigations of recent medical research will be discussed. Three sessions are planned for Friday and one for Saturday morning. Dr. Otto C. Brantigan, of Baltimore, is in charge of the program committee for the meeting.

Officers of the Eastern Section are Dr. Katharine R. Boucot, of Philadelphia, president; Dr. Norman J. Wilson, of Brookline, Massachusetts, vice-president; and Dr. Frederick Beck, of Ray Brook, New York, secretary-treasurer.

NEW YORK DIABETES ASSOCIATION

The Second Annual Symposium Day on Diabetes of the New York Diabetes Association will be held at the Memorial Center for Cancer and Allied Diseases, 444 East 68th Street, New York City, on Thursday, October 14, at 9:15 a.m. Physicians, medical students and other professional personnel interested in diabetes are invited to attend. No registration is necessary.

A dinner program will be held in the evening, when Ancel Keys, Ph.D., director, Laboratory of Physiological Hygiene, University of Minnesota, will speak on the subject "Relative Obesity and the Blood Chemistry in Man."

The evening program will be held at the New York Academy of Sciences, 2 East 63d Street, New York City.

MEMORIAL CENTER FOR CANCER AND ALLIED DISEASES CONFERENCE

The Strasburger Memorial Medical Foundation will sponsor a conference on recent and changing concepts in the diagnosis and management of cancers of the digestive tract in the auditorium, Memorial Center for Cancer and Allied Diseases, New York City, on November 12, from 9:30 a.m. to 1 p.m.

Reservations should be made through the office of the assistant clinical director, Memorial Center, 444 East 68th Street, New York 21, New York, before November 5, since the seating capacity is limited.

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

The fall meeting of the New England Society of Anesthesiologists will be held in Hanover, New Hampshire, at the Mary Hitchcock Memorial Hospital, Friday, October 8, beginning at 8:30 a.m. Further information may be obtained from Dr. Richard H. Barrett, Hitchcock Clinic, Hanover, New Hampshire.

SOCIETY MEETINGS AND CONFERENCES

SEPTEMBER 25 and 26. New England Conference on Cerebral Palsy. Hotel Statler, Boston.

SEPTEMBER 27 and 28. Consultation Clinics for Crippled Children in Massachusetts. Page 362, issue of August 26.

SEPTEMBER 27–DECEMBER 8. Postgraduate Seminar in Psychiatry and Neurology. Page 452, issue of September 9.

SEPTEMBER, 1954–APRIL, 1955. Postgraduate Medical Institute. Page 451, issue of September 9.

SEPTEMBER 30–OCTOBER 2. Canadian Society for the Study of Fertility. Page 285, issue of August 12.

OCTOBER 1 and DECEMBER 3, 1954; FEBRUARY 4 and APRIL 1, 1955. New England Society of Anesthesiologists. Page 1054, issue of June 17.

OCTOBER 4, 1954–JANUARY 17, 1955. Hartford Medical Society. Page 496, issue of September 16.

OCTOBER 6. Massachusetts Medical Society. Stated Meeting of the Council. Page 493, issue of September 16.

OCTOBER 7 and 8. Pan-Pacific Surgical Association. Page 1092, issue of June 24.

OCTOBER 8. New England Society of Anesthesiologists. Notice above.

OCTOBER 8 and 9. Academy of Psychosomatic Medicine. Page 748, issue of April 29.

OCTOBER 11–15. American College of Physicians Course. Page 44, issue of July 1.

OCTOBER 14. New York Diabetes Association. Notice above.

OCTOBER 16–22. American Occupational Therapy Association. Page 1092, issue of June 24.

OCTOBER 18–29. New York Academy of Medicine Graduate Fortnight. Page 44, issue of July 1.

OCTOBER 22. National Vitamin Foundation Symposium. Page 410, issue of September 2.

OCTOBER 22 and 23. American Trudeau Society (Eastern Section). Notice above.

OCTOBER 25–27. New England Postgraduate Assembly. Hotel Statler, Boston.

OCTOBER 25–27. National Gastroenterological Association. Page 496, issue of September 16.

OCTOBER 25–30. Course in Care of Atomic Casualties. Page 285, issue of August 12.

OCTOBER 27. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.

OCTOBER 27–29. International Symposium on the Hypophyseal Growth Hormone. Page 1092, issue of June 24.

OCTOBER 29. Massachusetts Public Health Association. Fall Meeting. Blake's Restaurant, Springfield, Massachusetts.

OCTOBER 31–NOVEMBER 4. American Institute of Dental Medicine. Page 968, issue of June 3.

NOVEMBER, 1954–MAY, 1955. Sanitary Engineering Center Training Programs. Page 122, issue of July 15.

NOVEMBER 2–5. Fourth Annual Bay State Rehabilitation Conference. Hotel Statler, Boston.

NOVEMBER 3 and 4. M & R Pediatric Research Conference. Page 496, issue of September 16.

NOVEMBER 3–5. National Society for Crippled Children and Adults. Page 44, issue of July 1.

NOVEMBER 6. Massachusetts Hospital School Symposium. Page 495, issue of September 16.

NOVEMBER 12. Memorial Center for Cancer and Allied Diseases Conference. Notice above.

NOVEMBER 12 and 13. Inter-Society Cytology Council. Page 968, issue of June 3.

NOVEMBER 15–19. American College of Surgeons. Page 496, issue of September 16.

NOVEMBER 15–26. Laboratory Diagnosis of Tuberculosis Course. Page 246, issue of August 5.

DECEMBER 5. American Academy of Dental Medicine. Page 1092, issue of June 24.

DECEMBER 8. New England Pediatric Society. Page 968, issue of June 3.

DECEMBER 13–17. Congress of Obstetrics and Gynecology. Page 748, issue of April 29.

JANUARY 3–MAY 9, 1955. Postgraduate Seminar in Psychiatry and Neurology. Page 452, issue of September 9.

JANUARY 10–15. Course in Care of Atomic Casualties. Page 285, issue of August 12.

FEBRUARY 7–9. McIntyre Saranac Conference. Page 410, issue of September 2.

FEBRUARY 11–25. Pan-American Academy of General Practice. Page 496, issue of September 16.

MARCH 7–12. Course in Care of Atomic Casualties. Page 285, issue of August 12.

MAY 4 and 5. American Psychosomatic Society. Page 286, issue of August 12.

JUNE 21–25. National Association for the Prevention of Tuberculosis. Page 540, issue of March 25.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, SEPTEMBER 30

THURSDAY, SEPTEMBER 30

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00–10:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*10:00–11:00 a.m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.

*10:00–11:00 a.m. Surgical Rounds. 5th floor teaching unit, Beth Israel Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*11:00 a.m. Thoracic Conference. Surgery of Aortic Insufficiency and Aortic Stenosis. Drs. Dwight E. Harken, Harrison Black and Lester Dexter. Main Amphitheater, Peter Bent Brigham Hospital.

*4:00–5:00 p.m. Pediatric Seminar. Burnham Memorial Hospital (Burnham 4), Massachusetts General Hospital.

FRIDAY, OCTOBER 1

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m. Clinical Conference. Premature Separation of Placenta. Dr. J. Whelton. St. Margaret's Hospital, Dorchester.

*11:00 a.m.–1:00 p.m. Medical Grand Rounds. Dr. Proger and Staff. Stearns Auditorium, New England Center Hospital.

*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.

*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.

*4:00–5:00 p.m. Child Psychiatry. Burnham Memorial Hospital (Burnham 4), Massachusetts General Hospital.

(Notices concluded on page xxiii)